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National Institutes of Health

*Annual
Report
of International
Activities*

*Fiscal Year
1981*

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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Annual Report of International Activities

*Fiscal Year
1981*

Prepared by
John E. Fogarty International Center
for
Advanced Study in the Health Sciences

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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NATIONAL INSTITUTES OF HEALTH ANNUAL REPORT OF INTERNATIONAL ACTIVITIES: FISCAL YEAR 1981 TABLE OF CONTENTS

	Page
Foreword	v
1. Highlights of Recent Scientific Advances.....	1
2. Summary of International Activities by Country.....	5
3. Fogarty International Center (FIC)	11
4. National Cancer Institute (NCI)	23
5. National Eye Institute (NEI)	35
6. National Heart, Lung, and Blood Institute (NHLBI).....	39
7. National Institute on Aging (NIA).....	53
8. National Institute of Allergy and Infectious Diseases (NIAID)	55
9. National Institute of Arthritis, and Digestive and Kidney Diseases (NIADDK)	67
10. National Institute of Child Health and Human Development (NICHD).....	71
11. National Institute of Dental Research (NIDR).....	75
12. National Institute of General Medical Sciences (NIGMS).....	77
13. National Institute of Environmental Health Sciences (NIEHS)	79
14. National Institute of Neurological and Communicative Disorders (NINCDS)	83
15. National Library of Medicine (NLM)	85
16. Clinical Center (CC).....	89
17. Division of Computer Research and Technology (DCRT)	91
18. Division of Research Resources (DRR)	93
19. Division of Research Services (DRS)	95

FOREWORD

On behalf of the Director of the National Institutes of Health (NIH) and the staff of the Fogarty International Center for Advanced Study in Health Sciences (FIC), I am pleased to present this 13th National Institutes of Health Annual Report of International Activities. Edited by the FIC, but based upon reports by each of the Bureaus, Institutes, and Divisions (BID's) of the NIH, this report provides an overview of recent health-related international activities relevant to the NIH mission and within the purview of one or more of the BID's.

The international programs of the NIH are authorized under the International Health Research Act of 1960 (P.L. 86-610) to "advance the status of the health sciences in the United States and thereby the health of the American people through cooperative endeavors with other countries in health research, research planning, and research training. . . ." But the benefits of NIH international programs extend far beyond our borders. Through cooperative relationships that the BID's have established in their intramural and extramural programs, foreign biomedical and behavioral research scientists have collaborated with their U.S. counterparts to advance knowledge leading to improved methods of treatment, control, and, ultimately, prevention of disease.

Since 1968, when the Fogarty International Center was created by the Congress, it has been the focal point for international facets of NIH activities. The number and kind of international programs differ from Institute to Institute, but the FIC is the only NIH component with an explicit international mission, which includes NIH-wide coordination of and liaison for activities relevant to this mission in addition to its specific international programs.

The international activities of the NIH have many goals, dictated by the objectives of the intramural and extramural programs of the categorical Institutes and the resource and service Divisions. Implementation of these goals must in turn be responsive to and consistent with national and international policies. The coordination and liaison functions of the Fogarty International Center are designed to serve as a resource for information from and to the Department of State, foreign embassies in this country, and multilateral organizations such as World Health Organization and Pan American Health Organization. At the same time, the international activities reflect changes in the health scene, as some diseases are reduced or controlled and

others present new and broader challenges. The NIH is also concerned with the emerging needs of and opportunities in developing nations and has established contacts that are described in this report.

As part of its coordinating function, the FIC was assisted by the BID's in providing the information for this report. A particular objective was that material be selected and presented in such a way that it would be useful for congressional purposes, would be of interest to scientists from abroad, and would provide specific examples of how international programs and activities have contributed to biomedical and behavioral research and national health in the U.S. It was also intended that information be conveyed in a fashion that would be intelligible to various audiences, including educated laymen, scientists who are not specialists in the area under discussion, and members of NIH councils and advisory groups. In a departure from past procedures, we asked the BID's to provide information under specific headings (for example, bilateral agreements, activities with international agencies). To present a relatively consistent format, we have taken some liberties with the reports submitted by the BID's. We have not altered the scientific material except to delete sections that were either not relevant to the goals of this report or were too detailed to be included.

Chapter I of the report highlights scientific advances resulting from recent collaborative efforts involving foreign and U.S. scientists. Chapter II provides information on a particular country, but does not include details which are covered elsewhere in the report. The remaining chapters were submitted by the BID's, but were edited for format and length. A table showing fiscal year 1981 total funding for NIH international programs is appended.

Within the limitations of a single report it is not possible to do justice to the complexities of the NIH international activities and to their contributions to betterment of health in the U.S. and abroad. We are, nonetheless, endeavoring to provide a document of interest and use to a variety of audiences and welcome comments that will enable us to achieve these objectives.

Mark S. Beaubien, M.D.

Acting Director, Fogarty International Center

*Acting Associate Director, Office of International Research
National Institutes of Health*

10-12-82

FY 1981 Total Funding for NIH Intern

(\$ in thousands)

February 25, 1982

I. Research Awards

A. Grants:

Regular Foreign Grants	3,8
Special Foreign Grants (GMI, IPCS, ICIDR)*	
Domestic Grants with Foreign Components	1,0
Special Foreign Currency (PL-480) Grants	2

B. Contracts:

Foreign Contracts	5,2
Domestic Contracts with Foreign Components	

II. Scientist Exchanges

A. Foreign Scientists in U.S.:

Visiting Associates, Scientists, Fellows	5,1
International Research Fellowships	
Fogarty Scholars	

B. U.S. Scientists Abroad:

Fogarty Senior Fellowships	
National Research Service Awards	
Foreign Work Study Assignments	

III. International Conferences

IV. International Travel

International Meetings	3
Multilateral Organization Activities	
Bilateral Exchanges	
Other	

V. BID Program Support

Bilateral Exchanges	3
Staff and Other	2

Totals	16,8
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Totals may not add due to rounding

* GMI — Gorgas Memorial Institute

IPCS — International Program on Chemical Safety

ICIDR — International Collaboration in Infectious Diseases Research

10-12-82

FY 1981 Total Funding for NIH International Programs — By Activity and BID

(\$ in thousands)
February 25, 1982

	NCI	FIC	NIADDK	NHLBI	NIAID	NINCDS	NICHD	NIEHS	NIDR	NEI	NIGMS	NIA	DRS	NLM	OC	DCRT	OD	DRR	Totals	NIH Funds	Other Funds
I. Research Awards																					
<i>A. Grants:</i>																					
Regular Foreign Grants	3,836	—	2,078	909	932	1,698	887	290	531	825	838	399	—	—	—	—	—	—	13,223	(13,223)	—
Special Foreign Grants (GMI, IPCS, ICIDR)*	—	1,800	—	—	2,585	—	—	400	—	—	—	—	—	—	—	—	—	—	4,785	(4,785)	—
Domestic Grants with Foreign Components	1,028	—	—	327	160	—	1,021	26	—	122	—	104	—	7	—	—	—	200	2,996	(2,996)	—
Special Foreign Currency (PL-480) Grants	225	—	4	26	188	129	26	227	—	31	—	—	—	55	—	—	—	—	911	—	(911)
<i>B. Contracts:</i>																					
Foreign Contracts	5,259	—	648	2,178	170	86	741	366	—	—	—	—	268	—	—	—	—	—	9,717	(9,717)	—
Domestic Contracts with Foreign Components	—	—	—	235	—	32	—	—	—	—	—	—	—	—	—	—	—	—	267	(267)	—
II. Scientist Exchanges																					
<i>A. Foreign Scientists in U.S.:</i>																					
Visiting Associates, Scientists, Fellows	5,162	—	2,437	815	876	1,536	932	864	903	285	6	405	131	47	90	71	—	—	14,568	(14,568)	—
International Research Fellowships	—	3,450	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,450	(3,450)	—
Fogarty Scholars	—	478	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	478	(478)	—
<i>B. U.S. Scientists Abroad:</i>																					
Fogarty Senior Fellowships	—	673	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	673	(673)	—
National Research Service Awards	54	—	97	112	44	323	62	21	55	58	258	—	—	—	—	—	—	—	1,084	(1,084)	—
Foreign Work Study Assignments	9	—	56	—	—	—	—	—	11	—	—	46	—	—	—	—	—	—	120	(120)	—
III. International Conferences	138	186	138	74	140	10	18	25	6	13	15	17	3	—	5	2	8	15	813	(813)	—
IV. International Travel																					
International Meetings	308	5	115	88	49	100	35	41	46	14	2	33	1	3	4	16	11	3	873	(467)	(406)
Multilateral Organization Activities	34	2	11	3	6	19	17	11	3	14	—	9	2	1	—	—	6	—	137	(17)	(155)
Bilateral Exchanges	46	14	7	31	20	10	33	6	—	24	—	—	15	3	—	—	2	—	210	(109)	(101)
Other	90	9	39	23	11	4	28	39	31	7	—	2	31	5	—	3	—	—	322	(164)	(123)
V. BID Program Support																					
Bilateral Exchanges	364	259	7	585	283	—	26	42	—	5	—	—	27	—	—	—	—	—	1,598	(1,598)	—
Staff and Other	270	2,232	90	196	83	98	88	79	81	12	—	26	24	188	46	—	15	—	3,528	(3,528)	—
Totals	16,823	9,108	5,727	5,602	5,547	4,045	3,914	2,437	1,667	1,410	1,119	1,041	502	309	145	92	42	218	59,753	(58,057)	(1,696)

Totals may not add due to rounding

* GMI — Gorgas Memorial Institute
IPCS — International Program on Chemical Safety
ICIDR — International Collaboration in Infectious Diseases Research

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES

The following highlights present a selective rather than exhaustive summary of scientific accomplishments under international research programs and activities sponsored by the Bureaus, Institutes, and Divisions (BID's) of the NIH. This summary has drawn upon detailed reports submitted by the BID's, but presents them in a different perspective. Whereas the BID's look at their international programs and activities in the context of their categorical missions, this section endeavors to view the accomplishments in the larger context of global health problems. In some instances, cooperative studies between the U.S. and other countries are reported although they have not yet been completed or provided definitive answers. They are, however, important because they are using innovative research approaches or new technologies, or are studying special populations. Hence, they are opening new paths to the solution of health problems of international concern.

Population studies are both difficult and costly to conduct in a fashion that provides reliable data and definitive answers. There are, however, populations in various parts of the world that have been valuable resources for the study of disease prevention and disease control using epidemiologic methods of investigation. Through their international research programs, the Institutes of NIH have engaged in cooperative epidemiologic studies with foreign countries when population groups provided features that were eminently suitable for learning about factors that cause or influence the course of a disease. In some instances, a population has been exposed to environmental factors rarely found elsewhere, or a population group with a uniform genetic background provides enough individuals with a genetically determined disease to be suitable for an epidemiologic study. In still other instances, a population's ethnic background makes it possible to learn the influence of such factors as dietary habits, behavior patterns, and lifestyles on the incidence and prevalence of disease. Recent accomplishments resulting from such studies are highlighted below.

A population study of interest is being conducted by NINCDS scientists in collaboration with scientists at the University of Zulia in Maracaibo, Venezuela. They are examining 200 patients with Huntington's disease and 2,000 of their relatives, because this population, descended from a single Spanish sailor who arrived in

the country in 1860, offers an opportunity to study a neurologic disease known to be hereditary and present in an unusually large number of individuals. Although Huntington's disease occurs in the U.S., it is relatively rare. The disease is similar in its manifestations to more common neurologic disorders, including Parkinson's disease. The Venezuelan patients have been given neurologic and psychologic tests, and their movements have been recorded on film. The study is promising not only because it is a source of information about inherited neurologic disorders, but also because the population under study may include descendants who carry two genes for Huntington's disease as a result of intermarriage.

In contrast to the genetic uniformity provided by the Venezuelan population is the population of Jerusalem, which is of interest because of the diversity of ethnic backgrounds of its residents. There are, in consequence, great differences in dietary patterns, lifestyles, education, and socioeconomic status. The origin of the population has been accurately recorded. Among the young people, 90 percent are known to have been born in Israel, whereas only 20 percent of their parents were native born. This population, therefore, provides the opportunity to study the effects of diverse environmental factors on a disease and to assess various risk factors. Both NHLBI and NIADDK are cooperating with Israeli scientists in studies of this population as described below.

The NHLBI, which has collaborated with many countries to collect data on environmental, familial, and genetic influences on atherosclerotic disease, has supported the establishment of a Jerusalem Lipid Research Clinic at Hadassah University Hospital that capitalizes on the resource available in the multiethnic population of Jerusalem. The study has screened more than 8,000 young people as part of their preinduction examination for military service, and about 7,000 of their parents. Preliminary data show important differences in dietary fat intake and blood lipid profiles that correlate with differences in the country of parental origin. The results thus far also provide clues to the relative roles of genetic factors and lifestyle in the etiology of cardiovascular disease. Of great interest is that Yemenites migrating to Israel suffered from malnutrition but not from diabetes or heart disease; but after a single generation on an Israeli diet, Yemenites began to develop both of these diseases. The fact,

however, that they did not develop diabetes or heart disease to the extent it developed in Israelis of European parentage indicates that genetic as well as environmental influences are involved.

Another study taking advantage of the opportunity to study the effect of dietary components on the manifestations of a disease in persons with different ethnic backgrounds is being conducted in Jerusalem by the Hebrew University of Jerusalem with support by NIADDK. The effects of prolonged administration of a combination of calcium, phosphate, and fluoride salts on bone density and structure are being studied in a middle-aged group of patients with osteoporosis.

Using funds available through the FIC Special Foreign Currency Program, the NHLBI is sponsoring a study in Poland with the Polish Academy of Sciences to determine the extent to which the main risk factors for coronary heart disease can be reduced in industrial workers. Preliminary data indicate higher blood pressure and cholesterol values in Warsaw than in Cracow, and a higher prevalence of cigarette smoking than in the U.S. Compared with the U.S., the Polish workers are more obese and have about the same prevalence of hypertension and considerably lower cholesterol levels.

A recent report of a collaborative study by NCI and Japanese scientists is another example of how a disease in a population group in a given locale may provide opportunities for research not possible in other populations. In this study, antibodies against an RNA tumor virus (retrovirus) were found in the blood of Japanese patients with adult T cell lymphoma but not in the blood of healthy persons from the same region or other parts of Japan. The type of T cell lymphoma under study occurs in fewer than 1 percent of all types of leukemia patients in the U.S. but is endemic in southwestern Japan, where it occurs in striking clusters on the islands of Kyushu and Shikoku. Antibodies to a virus have previously been demonstrated in animals with leukemia, but this is believed to be the first time such a relationship has been shown in human leukemia. These observations are not only of theoretical interest in relation to the etiology of cancer, but are also of possible clinical importance if a vaccine against the virus can be developed.

Although for most diseases epidemiologic studies reveal striking differences in incidence and prevalence in different geographic regions, this is not the case for one of the devastating alterations associated with aging; namely, Alzheimer's disease (senile dementia). A WHO world study has shown that about 6 percent of persons above age 65 are affected, and the prevalence is surprisingly consistent in different countries. The NIA and NINCDS have an interest in this disease and are examining the causes of the disability and the progressive degenerative changes that occur in populations in Canada, Holland, and Denmark. New test batteries have provided a finer dissection of cognitive versus memory disorders. Clinical, neurophysiological, biochemical, histopathological, and radiographic characteristics are being examined to determine the relationship between pathological changes and clinical manifestations. Some studies are concerned with regional alterations in brain metabolism that occur in

Alzheimer's disease, but thus far measurements have been made only on normal subjects.

An NEI epidemiologic study in Egypt that addresses prevention of blindness caused by trachoma, which is caused by an infectious agent (*Chlamydia*) found in the nose, throat, and feces, is also relevant to the interests of NIAID, because the same causative agent is associated with diarrheal disease and bronchitis in children. This type of blindness is more prevalent in Egypt than in countries of Western Europe and North America. The infectious agent is present in about 4.7 percent of the rural and 1.7 percent of the urban population of Egypt, but in no more than 0.2 percent of the population in the U.S. and Europe. When children are treated with antibodies against the infectious agent, and when hygienic measures are improved, trachoma as well as diarrheal disease and bronchitis are prevented.

NCI and NIAID have been sponsoring studies of a relationship between viral hepatitis and liver cancer (hepatoma), a relationship uncovered through epidemiologic studies in China (Taiwan), where hepatoma is the leading cause of death in males. Risk of developing this form of cancer was 340 times greater among carriers of hepatitis virus than among noncarriers, and 80 percent of patients with liver cancer showed the presence of hepatitis virus antigen. NIAID is supporting a clinical trial in China (Mainland) to assess the efficacy of a vaccine (developed in the United States) in preventing transmission of hepatitis virus to the neonate by mothers who are carriers. Because infected children are at risk of developing liver cancer in later life, the trial has important implications for the prevention of hepatoma. This is a problem of worldwide dimensions. Viral hepatitis affects almost one-half million persons in the United States, and 5 to 10 percent of these become carriers of the virus. In some parts of Southeast Asia and South Africa, as many as one in five persons test positive for the viral antigen. The array of Federal agencies that participated in this activity attests to the importance of this infectious disease and its relationship to other health problems. Sponsors of the International Symposium on Viral Hepatitis included the NIH Clinical Center and Blood Bank, the CDC, FDA, and NIAID, NCI, and FIC.

Among exogenous agents implicated in disease, nutritional factors have a pervasive role that is evident in reports of a number of Institutes. In some instances, dietary influences on a given disorder can be readily corrected once the critical factor has been identified. A noteworthy example is a reduction of bladder stone disease in children following identification of a nutritional deficiency. In Northeast Thailand, as in many developing countries, bladder stone disease is endemic in children, beginning as early as 1-year of age and peaking by age 3. An epidemiologic study of 21,000 individuals in this region of Thailand revealed oxalate crystalluria alone or with uric acid crystalluria in all age groups, but especially in children under 45 days. It occurred in 43 percent of these children, who also excreted very little phosphate in their urine. When an orthophosphate supplement was given in a small trial, the oxalate crystalluria disappeared within 24 hours in

children aged 6 to 19 months. In a subsequent more extensive 5-year trial supported by NIADDK, phosphated soda pop given 1,200 Thai infants and preschool children has led to a 60 percent reduction in bladder stone disease.

The role of nutrition in the control of hypertension and its sequelae has been the focus of a U.S.-Japanese study for some years. The importance of hypertension in the U.S. has been well documented through the NHLBI prevention program. In Japan, hypertension as a cause of stroke, which is a prevalent disease, is also of concern. Animal models developed in Japan have been useful tools for nutritional studies. A rat model of hypertension is available in the spontaneously hypertensive rat, and more recently, a stroke-prone spontaneously hypertensive rat model has been developed. Using the stroke-prone rat model, Japanese researchers have found a stroke-preventive effect of a dietary protein fed to animals with severe hypertension. The stroke-prone, spontaneously hypertensive rat had a lower incidence of stroke when fed the NIH rat diet than when given the standard Japanese diet. The protein to which the stroke-prevention effect is attributed includes sulfur-containing amino acids and certain aromatic amino acids. To be effective, the dietary intervention must be during the 3rd to 6th month of the animal's life, which is equivalent to ages 15 to 20 in man. There is now epidemiologic confirmation of the importance of dietary proteins in the development of stroke in Japanese population studies.

The interplay between scientific advances in the United States and abroad is well illustrated by some of the anticancer agents undergoing trials supported by NCI. Aclacinomycin A, an agent developed in Japan, has been shown to have good activity against leukemias and lymphomas (but not against solid tumors). It has undergone a Phase I (toxicity) trial and is now being studied in a Phase II (dosage) trial. Teroxirone, an anticancer agent that appears to be active against a variety of cancers, is undergoing a Phase I trial. Two analogs of anticancer agents (Adriamycin and Daunorubicin), produced by Italian scientists, are now undergoing preclinical testing because they appear to have less cardiotoxicity and to be active in a broader range of tumor systems than the agents now in use.

In a cooperative study by U.S. and Italian scientists, a device developed in the United States to aid in the treatment of acute respiratory distress syndrome is undergoing a clinical evaluation in both countries. Adult patients suffering from the usually fatal respiratory distress syndrome are being treated with an extracorporeal device that removes carbon dioxide, bringing the lung to rest, but allowing enough oxygen to diffuse through the motionless lung to maintain adequate oxygenation. Called "apneic oxygenation," the technique has shown sufficient promise in preliminary studies to warrant further exploration as a device to keep the patient alive until the lung has recovered sufficiently to resume its respiratory function.

Several recent studies exemplify how basic research can contribute to the clinical aspects of a disease problem. NIEHS and NCI scientists, in collaboration with scientists throughout the world, have developed

and validated 30 different short-term bacterial mutation test systems. This is of clinical importance because environmental agents capable of altering DNA within cells may have carcinogenic as well as mutagenic effects. Because it may be decades before a cancerous lesion due to an environmental agent has reached detectable dimensions, a test that can discriminate between carcinogens and noncarcinogens is of practical value. It also has implications for hereditary diseases because it detects DNA damage. The problem is complex because a number of factors are known to interact in determining the ultimate action of chemical mutagens and carcinogens. An example of such a factor is diet, as has been shown in a U.S.-Japanese cooperative study in which mutagenic and carcinogenic compounds have been identified and isolated from fried sardines and beef that have undergone alterations in the cooking process.

A U.S.-Chinese study of liver cancer supported by NCI provides another example of a basic study that may contribute to solution of a clinical problem: early detection of a disease. The investigation has drawn upon the availability of monoclonal antibodies, an availability that has resulted from dramatic recent advances in hybridoma technology. The study was triggered by the observation that aflatoxin, a toxic substance produced by a fungus (*Aspergillus*) that grows on peanuts and grains, is abundant in areas where liver cancer is prevalent.

Monoclonal antibodies to aflatoxin B₁ and aflatoxin B₁-adducts are being used to assess the effects of aflatoxin on cell metabolism and DNA damage in Chinese populations known to be at high risk of developing liver cancer. It is anticipated that antibodies to aflatoxin and its DNA adduct will be a useful biochemical marker of liver cancer and may contribute to earlier detection of this disease.

In a collaborative U.S.-Norwegian study of successive pregnancies, the NICHD reports that there is an association between perinatal mortality rates and the general tendency to repeat similar outcomes in successive pregnancies. For example, an underweight infant born to a woman who previously had given birth to a baby of normal size is at higher risk of perinatal death than an underweight infant born to a woman whose first infant was also underweight.

Although biomedical advances often have their inception in other countries, the U.S. is usually more conservative about adopting seemingly promising procedures until they have been clearly demonstrated to be both effective and without unwarranted or excessive side effects that are hazardous. An example is the trial being mounted in the U.S. to assess the efficacy of radial keratotomy, a surgical procedure to correct myopia that originated in the U.S.S.R. and is now being used in the U.S. with increasing frequency. Brought to this country by a physician who learned the procedure in the Soviet Union and trained others in its use, the procedure is now being assessed in a clinical trial supported by NEI to determine whether the reported beneficial effects persist, and whether damaging effects may manifest themselves later.

SUMMARY OF INTERNATIONAL ACTIVITIES BY COUNTRY

The NIH had some type of activity with 70 countries throughout the world in fiscal year 1981 through fellowships, grants, contracts, visiting scientists, and special foreign currency. This chapter summarizes activities for those countries with which there are formal bilateral agreements and for those with which there are a large number of informal scientific relationships. It is not intended to be a comprehensive description, of either the activities or the countries.

Argentina

A Science and Technology Agreement administered by the National Science Foundation is in effect. The Argentine Minister of Health designate visited NIH in February 1981 and discussed collaboration on research in Chagas' disease and coronary artery disease.

Australia

Although there is no formal agreement for collaboration with Australia, the following Institutes carry out cooperative programs with that country: DCRT, NIEHS, NICHD, NIDR, NIADDK, NEI, NIAID, NCI, NIGMS, and FIC. Australia is among the top 10 countries that successfully compete for NIH awards.

Brazil

An overall science and technology agreement was signed in 1971. There is no formal DHHS agreement. However, there have been useful relationships with Brazilian scientists and institutions over the years. The following Institutes participate in collaborative programs with Brazil: NLM, DRS, NIAID, NCI, and FIC.

Major activities being carried out in Brazil are:

- PAHO Regional Library of Medicine (BIREME) in São Paulo (NLM).
- Agreement between PAHO and Brazil to establish primate breeding and conservation programs (DRS).
- International Collaboration in Infectious Diseases (ICIDR) Program, consisting of various collaborative projects under the science and technology agreement between Brazil and U.S. institutions funded by NIAID.
- Collaboration with PAHO and BIREME in Latin American Cancer Information Project (NCI).
- Two NCI-PAHO Collaborative Cancer Treatment Research Centers in Rio de Janeiro and São Paulo.

Canada

Although there is no formal bilateral agreement with Canada, there is a great deal of interaction between NIH and Canadian scientists. Canada has been the recipient of more NIH awards than any other foreign country. FY 1981 awards exceeded \$8 million. The following Institutes support research projects in Canada: DCRT, NHLBI, NIEHS, NCI, NEI, NICHD, NIADDK, NINCDS, NLM, NIGMS, NIAID, NIA, NIDR, and FIC.

Egypt

An overall health agreement provides for a U.S.-Egypt Joint Working Group on Health Cooperation. Cooperative projects are being carried out in epidemiology and control of streptococcal infections; schistosomiasis; viral and posttransfusion hepatitis; microbiologic contamination of foods; laboratory management techniques in health care; and studies of bladder cancer. The following Institutes are involved in collaboration with Egypt: NLM, NIEHS, NCI, NINCDS, NICHD, NEI, and NIAID. Of particular interest to NIH is the high incidence of hepatitis, bladder cancer, schistosomiasis, and leishmaniasis, all of which provide opportunities for research not available in the U.S.

The following accomplishments have been reported:

- Completion of a joint project of population screening for urinary bladder cancer by urinary cytology in an endemic area of schistosomiasis (NCI).
- AID-funded program established by NIAID on malaria, Rift Valley fever, and leishmaniasis involving U.S. and Israel with Egypt.

Federal Republic of Germany

Bilateral relationships in the health field with the Federal Republic of Germany (FRG) are conducted under the agreement between DHHS and the Ministry of Research and Technology (MORT) of the FRG, commencing September 1976. A renewal of this agreement was discussed in July 1981 in Bonn. Participating Institutes are NCI, NHLBI, and FIC.

Highlights of recent accomplishments are:

- Cancer research activities in the fields of autovalent cytology, cytochemistry, and computer analysis.
- Development of a joint protocol for drug development and a testing program for cancer treatment.

●A joint workshop on Multiple Risk Factor Intervention Trials in cardiovascular disease held April 1981 in the FRG.

●U.S.-FRG Workshop in Bethesda to discuss cooperative activities relative to the German National Health survey as it relates to cardiovascular disease.

Finland

A draft Memorandum of Understanding between DHHS and the Finnish Ministry of Social Affairs and Health is under review.

France

The following agreements with France govern cooperation between the two countries: NIH-INSERM Agreement—exchange of letters between the Director of the NIH and L'Institut National de la Santé et de la Recherche Médicale (INSERM) for cooperation in the biomedical sciences (1969); NCI-INSERM Agreement for expanded cooperation in cancer research (1975); NLM-INSERM Agreement for on-line bibliography data bases (1974); NIH-French National Center for Scientific Research (CNRS) Agreement for support of exchange visits of scientists (1978). Both the INSERM and CNRS awards are administered by FIC. Institutes that participate in activities with France are NCI, NHLBI, NIADDK, NLM, and FIC.

The following accomplishments have been reported:

- Research progress in the area of pulmonary interstitial disorders (NHLBI).
- Basic and clinical research studies (NCI).
- Continued cooperative study of structure and mechanics of thyroid hormones (NIADDK).
- Agreement that scientist exchange under the NIH-CNRS accord was mutually beneficial.
- One Scholar-in-Residence (FIC).

Greece

An agreement for cooperation in science and technology was signed April 22, 1980. Under this agreement, a working group on scientific and technological cooperation was established. At the first meetings on October 2-3, 1981, the U.S. agreed to explore the interests of its agencies in holding joint symposia with Greek counterparts on one or all of the following topics:

- Nutritional factors in disease (e.g., cardiovascular, cancer).
- Emergency health services.
- Molecular biologic aspects of malignant neoplasia.
- Congenital hemoglobinopathies.

Hungary

An agreement between the Governments of the Hungarian People's Republic and the U.S. on Cooperation in Culture, Education, Science, and Technology was signed April 6, 1977. A Memorandum of Understanding with NCI for a cooperative cancer program was signed February 23, 1981. Priority areas are epidemiology, experimental pathology, immunology,

and therapy. NCI, NHLBI, and NINCDS have or are in the process of developing Institute-to-Institute or project-level relationships under the framework of the U.S.-Hungary Agreement. The Hungarian Government has agreed to the exchange of individual health scientists at a level of 12 man-months per year for each side.

India

An overall science and technology agreement with India is implemented by the Scientific Working Group on Medical and Health Sciences of the Indo-U.S. Sub-Commission on Science and Technology. The following cooperative projects are being carried out: determination of the safety and efficacy of contraceptive measures; increased understanding of the relationship between nutrition and blindness and the means of preventing blindness; and improving methods for preventing and treating filariasis. The following Institutes participate: NICHD, NLM, NEI, NCI, NINCDS, NIAID, NIA, NIADDK, DRR, and FIC.

Highlights of accomplishments are listed below:

- Agreement to establish a Center for Research on Nutritional Blindness in Hyderabad.
- Joint workshop on "Reproduction and Contraceptive Research" held in Bethesda.
- Establishment of a Reagent Bank for Reproductive Biology Research in India.
- Development and testing of new contraceptives.
- Strengthening of capabilities for research in clinical epidemiology.
- Hybridoma workshop.
- DRS senior staff member assigned to U.S. Embassy in New Delhi to assist the Science Counselor in health issues.

Israel

The U.S.-Israeli Binational Science Foundation was created to pool the remaining U.S. Special Foreign Currency resources and matching Israeli funds when Israel was removed from the "excess foreign currency" list. NIH provides technical opinion on research projects submitted to the Foundation for funding. A U.S.-Israel Health Agreement was signed in 1980. Priority areas will be established in the near future. Israel's high level of scientific development and excellent institutions are conducive to very productive scientific collaboration. The following Institutes have established collaborative projects with Israel: NHLBI, NIADDK, FIC.

Recent accomplishments are:

- Establishment of Lipid Research Clinic in Israel by NHLBI.
- Cooperative study by NIADDK on bone diseases.
- Five Scholars-in-Residence.
- U.S. AID-funded program established on malaria, Rift Valley fever, and leishmaniasis involving U.S., Egyptian, and Israeli scientists.

Italy

There are two separate agreements with Italy for

cooperation in science and technology. Collaborative areas are biomedical communications; health aspects of environmental pollution; cardiovascular diseases; U.S.-Italy cancer program; cell biology and immunology; and mental health. The following Institutes participate in the agreements: NLM, NIEHS, NHLBI, NCI, and NIAID.

Accomplishments that have been reported are:

- Workshop on "Clinical Biomedical Pharmacology," November 1980, on opportunities for collaborative studies.
- Symposium on "Nutrition and Cardiovascular Disease," December 1980, explored role of nutrition in development and prevention of cardiovascular disease.
- U.S.-Italy Joint Committee meeting held in Bethesda, November 1980.
- Partial support by NCI of Coordinating Center for Melanoma, National Institute of Oncology, Milan.

Japan

Bilateral relationships with Japan in the health field are encompassed under several distinct agreements or arrangements: U.S.-Japan Cooperative Medical Science Program (JCMSP); U.S.-Japan Cooperative Cancer Research Program; U.S.-Japan Cooperative Program on Vision Research; U.S.-Japan Program for Science and Technology (Non-Energy) Cooperation; and Agreement between the U.S. National Library of Medicine and the Japan Information Center for Science and Technology for input to the NLM MEDLARS data bank. Institutes participating in the agreement are NCI, NHLBI, NIAID, NEI, NIADDK, NIEHS, DRS, NLM, and FIC.

Some accomplishments under these relationships are:

- Seventeenth Meeting of the Joint Committee of the U.S.-Japan Cooperative Medical Science Program held in July 1981.
- Publication of a third 5-year report on the U.S.-JCMSP (1975-80).
- Identification of specific areas of mutual interest related to recombinant DNA research.
- A handbook, near completion, on genetic monitoring of laboratory animals.
- One Scholar-in-Residence.

Kenya

A Memorandum of Understanding for Scientific and Technical Cooperation was signed in September 1980, and the areas of cooperation related to it will be identified in the future.

Kuwait

A bilateral agreement between DHHS and the Ministry of Public Health of Kuwait for Technical Cooperation Programs in Health was signed May 8, 1981. The agreement is primarily a vehicle by which Kuwait would obtain technical services or consultation from the U.S. on a reimbursable basis. In the only activity in FY

1981, NHLBI was requested to provide names of consultants for a program to be developed in hypertension prevention and control.

Mexico

There is no formal bilateral agreement with Mexico. A joint communique was signed in 1981 for the continuation of the U.S.-Mexico Border Initiative, but NIH has not participated in this as yet. The NINCDS and the Institute of Neurology, Mexico City, are both WHO-designated Collaborating Centers for Research and Research Training in the Neurological Disorders. A collaborative protocol has been established between the two institutions for research and research training in the areas of epilepsy and stroke. Additionally, a small pilot program in neuroimmunology has been established.

Nigeria

A Memorandum of Agreement for Health Cooperation was signed in 1981, under which Nigeria will reimburse the U.S. for projects that are of benefit to Nigeria. Cooperation in the following areas has been proposed: tropical diseases; cancer; cardiovascular disease; hemoglobin disorders; and dental/oral diseases and nutrition. There is interest on the part of many Institutes, and plans are being formulated. NIEHS and National Institute of Occupational Safety and Health will share responsibility for cooperation in environmental and occupational health. The first meeting of the Joint Working Group on Health Cooperation was held in February 1981.

People's Republic of China

The U.S.-PRC Protocol for Cooperation in the Science and Technology of Medicine and Public Health has been in effect since June 1979. Cooperative projects have been established in infectious and parasitic diseases; cancer; cardiovascular diseases; public health and health services research; child health and nutrition; environmental and occupational health; medical information science; immunology; medical genetics; mental health; food and drugs, including pharmacology; and reproductive physiology and family planning. Institutes participating in the protocol are NCI, NHLBI, NIAID, NICHD, NIEHS, and NLM.

The following accomplishments have been reported:

- The second Joint Health Committee Meeting in Tianjin, China, November 1980.
- Agreement to test hepatitis B vaccine in China.
- Agreement to conduct a major epidemiologic study of cardiovascular disease in selected populations in China.

Poland

Under a bilateral agreement between the Governments of the U.S. and the Polish People's Republic, on Cooperation in the Field of Health, signed in October 1974, a joint oversight committee (DHHS and Polish Ministry of Health) approves health projects supported

by the Joint Fund for Science and Technology. These activities are a followup to Special Foreign Currency projects. A U.S.-Poland Individual Health Scientist Exchange Program is administered by FIC on behalf of Public Health Service (PHS) agencies.

There is scientific collaboration on more than 30 projects in the health field. Participating Institutes are NHLBI, NICHD, NLM, NIADDK, NINCDS, and FIC. There are 13 institute-to-institute agreements involving both Federal and non-Federal health research institutions.

Listed below are highlights of U.S.-Polish collaboration.

- Symposium on "Ischemic Heart Disease," arranged jointly by the National Institute of Cardiology, Warsaw, and the NHLBI, March 1981, in Bethesda.

- Agreement for Cooperation in Cancer Research between NCI and the Maria-Sklodowska-Curie Memorial Institute of Oncology, renewed in April 1981.

- Fifth Annual U.S.-Polish Medical Week, held October-November 1980 in Bethesda, focused on pediatrics. Visiting delegation led by representatives from the National Research Institute for Mother and Child, Warsaw.

Romania

An agreement between the Government of the United States of America and the Government of the Socialist Republic of Romania on Cooperation and Exchanges in the Cultural, Education, Scientific and Technological Fields was signed December 13, 1974. Joint workshops conducted at NIH in 1979 and in Romania in 1980 identified immunology and metabolic activity as they relate to cancer and cancer-causing agents as areas for future collaboration.

The U.S.-Romania Individual Health Scientist Exchange Program, administered by FIC for all PHS agencies, falls under the agreement for science and technology, and sponsors exchange visits of health scientists.

Spain

A complementary agreement on scientific and technological cooperation with Spain is expected to be signed in the near future. The Public Health Service has sent an expert team to Spain to consult with Spanish authorities on health problems associated with chemically contaminated cooking oil.

Sweden

NIH research relationships with Sweden have been close and active over many years, although there is no formal cooperative agreement. The high quality of biomedical institutions and investigators in Sweden and the openness of their international relationships have allowed for this degree of interchange without the need for formal agreement. Sweden has ranked among the four or five countries most successful in competing for NIH awards. Sweden offers five or six research fellowships each year to young U.S. scientists for work in Swedish laboratories; FIC screens and nominates the

fellowship candidates. The following Institutes make awards to Swedish scientists and institutions: NCI, NIA, NIADDK, NIDR, NINCDS, NHLBI, NEI, and FIC.

Switzerland

While there is no formal agreement for cooperation between the NIH and Switzerland, there is frequent and active collaboration. Switzerland ranks within the top 10 countries competing successfully for NIH awards. Switzerland offers fellowships to promising U.S. scientists for study in Switzerland; FIC screens and nominates candidates. The following Institutes make awards to Swiss scientists and institutions: NIAID, NCI, NEI, NIADDK, DCRT, NIDR, and FIC.

Taiwan

Under the Taiwan Relations Act (P.L. 96-8, 1979), the American Institute in Taiwan (U.S.) and the Coordination Council for North American Affairs (Taiwan) signed the Cooperative Science Agreement on September 4, 1980. The Division of International Programs, National Science Foundation, accepted the leading role in promoting scientific and scholarly cooperation on January 27, 1981. There are currently no cooperative projects. However, in FY 1981, one Taiwanese scientist was a Fogarty Scholar-in-Residence.

Union of Soviet Socialist Republics

Cooperation between NIH and counterpart agencies in the Soviet Union takes place under three agreements: Agreement for Cooperation in Medical Science and Public Health, Agreement for Cooperation in Artificial Heart Research and Development, and Agreement for Cooperation in the Field of Environmental Protection. An individual health scientist exchange program with the Soviet Union is administered by FIC for the Public Health Service.

The following accomplishments have been reported:

- Testing and evaluation of Soviet anticancer drugs by U.S. scientists.
- Collection of information on risk factors contributing to cardiovascular disease and on treatment of advanced coronary heart disease.
- Testing of artificial heart devices.
- Joint clinical trials using Soviet-developed Q-switched laser in treatment of glaucoma.
- Exchange of information and virus isolates enabled U.S. public health specialists to prepare better for influenza epidemics.
- Information on possible health impacts of oil shale production and electromagnetic radiation effects was made available to U.S. scientists.

United Kingdom

Although there is no formal agreement for cooperation with the United Kingdom, there is frequent and active cooperation between scientists. NCI, NHLBI, and FIC have collaborative programs with the United Kingdom.

Some recent accomplishments are:

- Cooperation between NHLBI and Britain in the development of a computer-based chemical information system; the British-Norwegian Migrant Study to assess the prevalence of "angina" and other cardiorespiratory symptoms; and the European Trial in Multifactorial Prevention of Coronary Heart Disease.
- Cooperative preclinical and clinical research associations between U.S. and U.K. cancer centers, stimulated by and with partial support from NCI.
- One Scholar-in-Residence.

Venezuela

An agreement for Scientific and Technological Cooperation in Health between DHHS and the Venezuelan Ministry of Health was signed August 11, 1980. The following cooperative projects are planned: systems for maintenance of scientific equipment and research on infectious diseases including leprosy, Chagas' disease, diarrheal diseases, and cardiovascular diseases. NIAID, DRS, FIC, NHLBI, and NINCDS have or plan to carry out programs with Venezuela.

Yugoslavia

An agreement between the Governments of the U.S.

and the Socialist Federal Republic of Yugoslavia on Scientific and Technological Cooperation was signed May 18, 1973. The agreement established the U.S.-Yugoslavia Joint Board on Scientific and Technological Cooperation and Joint Fund administered by the Board. An individual health scientist exchange program is supported by the Joint Fund and administered on the U.S. side by FIC. The following Institutes have ongoing collaborative programs with Yugoslavia: NLM, NHLBI, NINCDS, NICHD, and FIC.

The following accomplishments have been reported:

- Long-term prospective study of cardiovascular disease in a large population of Yugoslav men supported by NHLBI. Six joint publications have resulted.
- Epidemiologic followup study of secular trends on coronary heart disease risk factors in Yugoslavia.

Zimbabwe

A Science and Technology Agreement was signed in September 1980, under which NIH initiated discussions with the Zimbabwe Ministry of Health for cooperation in biomedical research.

JOHN E. FOGARTY INTERNATIONAL CENTER FOR ADVANCED STUDY IN HEALTH SCIENCES

Introduction

The Fogarty International Center (FIC) was created by an act of Congress in 1968 to provide a focus and an organizational mechanism for the role of NIH in international cooperation in all aspects of biomedical research.

The mission and objectives of the Fogarty International Center are to:

- Provide the facility for the assembly of scientists and leaders in the biomedical, behavioral, and related fields for discussion, study, and research relating to the development of science internationally as it pertains to health and its implications and applications for the future.
- Further international cooperation and collaboration in the life sciences through its research programs, conferences, and seminars.
- Provide postdoctorate fellowships for training in the United States and abroad and promote exchange of senior scientists between the United States and other countries.
- Coordinate the NIH activities and functions generally concerned with the health sciences at an international level.
- Serve as a focal point for foreign visitors to the National Institutes of Health.

In addition to the conduct of its particular programs, the FIC serves a central coordinating and integrating function for the international aspects of biomedical and behavioral research of the NIH, and as a major source of advice to the NIH Director on all matters related to international health. The Center maintains liaison with other components of DHHS, the Department of State and other Federal agencies, foreign embassies, and multinational and foreign organizations. On international issues and activities, the FIC must interact with each of the major Bureaus and Institutes of NIH as well as other cross-cutting Bureaus, Institutes, and Divisions. The Director, FIC, represents the Director, NIH, in providing policy guidance to, and participating with, the Institutes in the negotiation of formal agreements of cooperation with other governments and international organizations.

The FIC carries out its mission under five pro-

grams: the Advanced International Studies Program; International Research and Awards Programs; NIH Foreign Scientists Assistance Program; Special Foreign Currency and Joint Fund Programs; and International Coordination and Liaison Program. It also provides core support for the Gorgas Memorial Laboratory in Panama. These programs and activities for FY 1981 are described below.

Advanced International Studies Programs

The FIC contributes to advanced studies in the health sciences through three interrelated programs: the *International Issues Study-Program*, *International Conferences Program*, and *Scholar-in-Residence Program*. These have the same broad goal: to bring the knowledge and ideas of experts to bear on the identification of health-related issues of international importance and concern, and to develop strategies that will have a worldwide impact on prevention and control of diseases in the United States as well as abroad. They provide opportunities for the development of plans for activities that will have an impact on international health, for exchange of knowledge and ideas, and for intellectual stimulation.

International Issues Study-Program

The International Issues Study-Program is a new program under development. It addresses problems concerning international aspects of biomedical and behavioral research, research manpower training, and the transfer of research results to bring new knowledge to bear where it will benefit international health.

The following studies and activities were in various stages of planning in 1981:

- *International Symposium on Measles Immunization*: An organizing committee was established which involved FIC and representatives from WHO; PAHO; the Centers for Disease Control (CDC); NICHD; NIAID; Bureau of Biologics; FDA; USAID; Institute of Medicine; and the American Public Health Association. An international symposium will be held March 16-19, 1982, at which the following topics will be discussed: the socioeconomic and medical impact of measles

throughout the world; current immunizing materials and programs; further research; and the programs and efforts needed to bring measles to the point at which eradication will be possible.

●*International Symposium on Control of Poliomyelitis and the Feasibility of Eradication:* An organizing committee has been established with members from FIC; WHO; PAHO; Institute of Medicine; CDC; Bureau of Biologics, FDA; USAID; NIAID; NICHD; NINCDS; and the University of Washington School of Public Health. The planned symposium will look at the impact of poliomyelitis through the world, and a consensus will be reached on measures to be taken for the eradication of poliomyelitis. The resulting publication will provide guidance for international health organizations and the national health services of all countries.

●*The Use and Abuse of Antibiotics:* Current procedures in many countries for the distribution and use of antibiotics are giving rise to a growing number of strains of disease organisms resistant to the lethal effects of antibiotics, thus reducing the effectiveness of classical treatments for a number of important diseases. Preliminary discussions occurred with representatives of the PAHO, the Institute of Medicine, and several of the mission-related Institutes at NIH about the development of an international project concerned with this subject.

●*Task Force on Standardization of Nomenclature and Diagnostic Procedures for Digestive Diseases:* The NIH Coordinating Committee on Digestive Diseases requested FIC to undertake this project after considerable discussion as to its nature and importance. A Digestive Diseases Task Force Steering Committee was set up by FIC to plan the project, and the planning process is likely to continue through FY 1983.

A study is identified as an international issue if it meets the following criteria:

- Involves more than one country.
- Requires cooperation among various countries to solve the problems.
- Benefits the U.S. if the problem is solved.
- Is appropriate to the NIH mission.
- Has a feasible solution in light of the present state of knowledge and appropriate resources.

The operational strategy of the International Issues Study-Program is to: identify international health issues that should receive the attention of the categorical Institutes as well as the FIC; bring together experts to formulate questions to be answered in identifying and selecting alternative programs or activities; and bring together experts to develop an operational plan for actions by the FIC, appropriate NIH categorical Institutes, or other Federal agencies.

Various support mechanisms are to be used which are characterized by sponsorship by a number of national and international organizations, including WHO and PAHO, and participation by scientists and authorities from a number of countries.

The Study-Programs, administered by FIC staff, draw upon the expertise of the Scholars-in-Residence Program, scientists within the various categorical

Institutes of the NIH, as well as outside groups and consultants to formulate recommendations and plans.

International Conferences Program

The International Conferences Program fosters advanced international studies in the health sciences through meetings and conferences that provide opportunities for biomedical and behavioral scientists from various parts of the world to share their knowledge, ideas, and concerns about international health, and to evaluate ongoing research.

In 1981, five intramural conferences were organized by Scholars-in-Residence and NIH scientists working together. These were:

- "Symposium on Current Topics in Biostatistics and Epidemiology."
- "International Task Force on Animal Models Appropriate for Research on Diabetes."
- "International Symposium on the Contributions of Chemical Biology to the Biomedical Sciences."
- "International Symposium on Acclimatization, Adaptation, and Tolerance to High Altitudes."
- "Conference on Cytochemical Methods in Neuroanatomy."

The FIC also supports international aspects of extramural conferences that have been submitted to NIH as conference grant applications. These applications are reviewed by a peer group for scientific merit, and by an FIC panel for international importance in evaluation of funding. Of the 68 extramural conferences partially sponsored by FIC, 23 were held overseas, and the rest were in the U.S., Canada, or Mexico. They covered the broad field of biomedical and behavioral research, including fundamental research, clinical studies, and developmental research.

Several conferences are of particular note:

●*1981 International Symposium on Viral Hepatitis, March 20-April 2, 1981, New York, New York:* Perhaps no other scientific area has advanced as rapidly as that of viral hepatitis. Within a period of 15 years, the detection of a then-unidentified antigen (Australian antigen) has led to landmark discoveries. Major highlights of this meeting were the results of immunization research. A highly effective hepatitis B vaccine has been developed; a prototype hepatitis A vaccine is nearly ready for clinical trials; and a hyperimmune hepatitis B globulin, which is given to infants usually within an hour of birth, proved to be efficacious even when the mothers were carriers of hepatitis. Research presented at the symposium indicated that, overall, the HBV vaccine was extremely safe, highly immunogenic, and almost perfectly active among those who responded with the development of antisurface antibody.

●*Tenth International Narcotic Research Conference: Advances in Endogenous and Exogenous Opioids, July 26-30, 1981, Tokyo, Japan:* The Tenth International Narcotic Research Conference in Japan was considered the most important and definitive annual meeting dealing with the frontiers of the state-of-the-art in research on opiate receptors and opioid peptides. This international conference received a funding contribution from National Institute on Drug Abuse (NIDA), NIMH, NCI,

and FIC and was attended by scientists from 20 countries.

●*The Third International Conferences on Environmental Mutagens, September 21-27, 1981, Tokyo, Japan:* The FIC in conjunction with NCI, NIEHS, and the U.S. Environmental Protection Agency (EPA) provided partial financial support for the Third International Conference on Environmental Mutagens, which attracted participants from 33 nations.

An understanding of the extent to which results from *in vitro* tests can be extrapolated to the human situation remains rudimentary. The research trend is toward direct assays for mutagenic effects in somatic and germ cells of laboratory mammals and humans. However, it was noted that a fuller understanding of the effects of chemical mutagens on the somatic and germ cells of laboratory animals is essential in order to predict with some confidence the risk that exposure to a given chemical will represent.

●*Genetic Variation Among Influenza Viruses, March 8-13, 1981, Salt Lake City, Utah:* To foster better understanding of the mechanism of genetic variation among the influenza viruses and how to cope with it, this major international meeting was sponsored in part by NIAID, BOB/FDA, FIC, and CDC. Reports at the conference concerned attempts made, using recombinant DNA technology and rapid DNA sequencing techniques, to elucidate the variation at the levels of the nucleotide sequence of individual genes, and how such a sequence variation is translated into antigenic variation by changes in the amino acid sequence of viral proteins.

●*International Conference on the Biology of the Interferon System, April 21-24, 1981, Rotterdam, The Netherlands:* A critical impediment to the study and therapeutic use of the interferons has been a shortage of this rather expensive material. A demand for more and better purified interferon preparations has motivated a number of research groups to address themselves to the problem of interferon production. The technologies of large-scale tissue culture and of recombinant DNA are being successfully applied, and a large body of data, in need of critical review and discussion, has accumulated on the international science scene. NCI, NIAID, and FIC provided sponsorships and partial funding support for the conference that addressed this issue.

No firm conclusions can as yet be drawn regarding true percentages of response under any given regimen of treatment, or potential benefit to patients, or relative efficacy of interferon treatment when compared with other therapies. The need for substantial antiviral and antitumor trials in man clearly emerged from the clinical work reported at the international conference. Advances in several areas are progressively reducing the high cost of interferon so that the cost of its use in treatment, even against cancer, may very soon compare favorably with the cost of some other therapies.

●*Recent Developments in the Genetics of Insect Disease Vectors, April 20-24, 1981, Lake Como, Italy:* Five of the six major diseases of mankind (i.e., malaria, filariasis, schistosomiasis, trypanosomiasis, and leishmaniasis) are vector-borne; only leprosy is not. The World Health

Organization has estimated that these great parasitic diseases affect more humans directly (via disease processes) or indirectly (via economic processes) than any other form of disease. The developing countries of the tropical world are principally affected. Malaria is the most important disease in at least 70 countries, with over 400 million cases reported annually. In the last 5 years there has been a general worldwide increase of up to threefold in malaria cases.

To address this problem, and its possible solution, the FIC, NIAID, and the U.S. Department of Agriculture provided support and partial funding for an international meeting of leading geneticists on the insect vectors that transmit these diseases. The conference participants represented countries and research from almost all countries of the world.

Scholars-in-Residence Program

The purpose of the Scholars-in-Residence Program is to enable established scientists and scholars interested in international health to exchange information and ideas through preparation of a book, monograph, or other report; arrange meetings to foster interaction with other scholars and scientists; and collaborate in research in an environment conducive to innovative approaches to international health issues.

Scholars-in-Residence may be nominated by NIH scientists or former Fogarty scholars. Nominees are reviewed by an NIH panel of senior intramural scientists. Approved nominees are invited by the FIC as openings in the program become available.

Since 1970, 97 scholars from 21 countries have participated in the program. During FY 1981, 22 scholars participated for varying periods of time as shown below.

Of the 22, 8 were U.S. citizens, the others came from Sweden (2), U.K. (1), Israel (5), France (2), China (1), Japan (1), and Taiwan (1). These numbers represent the continued expansion of the program begun in FY 1979 and FY 1980 aimed at achieving a steady state of 10 Scholars-in-Residence at any given time. The average stay was 5 months, but the majority (11) of the Scholars were in residence for 3 months. Six Scholars stayed for 7 months or longer. Nine of the 22 were returnees; the rest were new to the program.

All of the Scholars have participated regularly in the intramural research seminars at the Stone House conducted by the Senior Science Advisor to the Office of the Director, NIH. They also met regularly throughout the year for a brown-bag lunch journal club at which they discussed their work and shared their perceptions of contemporary research programs.

Three major conferences in the Advanced Study Program organized by Scholars-in-Residence took place during 1981. The first of these, organized by Professor Carlos Monge, Cayetano Heredia Universidad, Lima, Peru, was a "Symposium on Acclimatization, Adaptation, and Tolerance to High Altitude." The second, organized by Drs. Sanford Palay and Victoria Chan-Palay, Harvard Medical School, Boston, was devoted to "Cytochemical Methods in Neuroanatomy." The third meeting was a workshop on "Affinity and Photoaffinity

Scholars-in-Residence During FY 1981¹

Dr. Herman Kalckar
Professor of Chemistry
Boston University, U.S.A.

Dr. Rolf Luft
Professor of Medicine
Karolinska Institutet, Sweden

Dr. David Shemin
Chairman
Dept. of Biochemistry & Molecular Biology
Northwestern University, U.S.A.

Dr. Bracha Ramot
Professor of Medicine and Head, Department of
Hematology
Chaim Sheba Medical Center
Tel Aviv University, Israel

Dr. Howard Schachman
Professor of Molecular Biology
University of California, U.S.A.

Dr. Jerard Hurwitz
Professor and Chairman
Developmental Biology and Cancer
Albert Einstein College of Medicine, U.S.A.

Dr. Hsiang-Tung Chang
Director
Shanghai Brain Research Institute
Academy of Sciences, People's Republic of China

Dr. Marianne Grunberg-Manago
Director of Research, C.N.R.S.
Head, Department of Biochemistry
Institut de Biologie Physico-Chimique, France

Dr. Sanford Palay
Professor of Anatomy
Harvard Medical School, U.S.A.

Dr. James Metcalfe
Professor of Biochemistry
University of Cambridge, U.K.

Dr. Carlos Monge
Rector
Cayetano Heredia Universidad, Peru

Dr. Sidney Bernhard
Professor of Molecular Biology
University of Oregon, U.S.A.

Dr. Franklin Bunn
Director, Hematology Division
Peter Bent Brigham Hospital, U.S.A.

Dr. Susan Lowey
Professor of Biochemistry
Rosentiel Basic Medical Science Research Center
Brandeis University, U.S.A.

Dr. Nathan Sharon
Head, Department of Biophysics
The Weizmann Institute of Science, Israel

Dr. Meier Wilchek
Professor of Biophysics
The Weizmann Institute of Science, Israel

Dr. Haruaki Yajima
Professor of Pharmaceutical Chemistry
Faculty of Pharmaceutical Sciences
Kyoto University, Japan

Dr. Giorgio Bernardi
Director of Research
Institute of Molecular Biology
National Center for Scientific Research, France

Dr. Hans Lindner
Chairman
Department of Hormone Research
The Weizmann Institute of Science, Israel

Dr. Tomas Hokfelt
Professor, Department of Histology
Karolinska Institutet, Sweden

Dr. Shmuel Shaltiel
Dean, Feinberg Graduate School
The Weizmann Institute of Science, Israel

Dr. Chen-Yuan Lee
Dean, College of Medicine
National Taiwan University, Taiwan, China

¹ Funds may have been obligated in FY 1981 or in previous fiscal years

Labeling," organized by Dr. Meier Wilchek, Weizmann Institute, Israel, in collaboration with the NIH Peptide Discussion Group. This meeting, involving mostly NIH staff, considered the latest techniques for identification and characterization of biologically active molecules in tissues and in the circulation. It has wide implications for application to the study of cell function, using monoclonal antibodies, and to the elucidation of immunologic defense mechanisms against disease-causing organisms.

International Research and Awards Program

The Fogarty International Center has always viewed as one of its most important functions the sponsorship of opportunities for U.S. scientists to work abroad and for foreign scientists to work in the United States for limited periods of time in direct collaboration. Such experiences broaden horizons, stimulate innovation, permit cost-effective sharing of resources, and upgrade scientific skills. Through cooperative arrangements with other countries and international organizations, the Center administers fellowship and exchange programs involv-

ing both U.S. and foreign scientists at the various levels of postgraduate experience.

There are four fellowship programs which are supported fully or partially by the FIC. These are the: International Research Fellowships; Senior International Fellowships; WHO/NIAID International Tropical Diseases Fellowships; and WHO/NINCDS/FIC International Neurosciences Fellowships. There are three other fellowship programs which are administered by the FIC but are supported by the Governments of France, Switzerland, and Sweden. These programs are the: French National Institute of Health (INSERM) Fellowships; Swiss National Science Foundation Fellowships; and Swedish Medical Research Council Fellowships.

International Research Fellowships

The International Research Fellowship Program (IRFP) provides opportunities for postdoctoral biomedical or behavioral scientists who are in the formative stages of their research careers to extend their research experiences in a laboratory in the United States. These fellowships serve to forge relationships between distinguished scientists in the United States and qualified scientists in other countries in order to resolve health-related problems of mutual interest.

During FY 1981, there were 44 participating countries with National Nominating Committees. Thirty-seven National Nominating Committees selected 129 applicants for the program. Of this number, 96 (78.74 percent) were funded. Recipient countries of fellowship awards are shown below.

1981 International Research Fellowship Awards by Country of Applicant

Americas	14	Taiwan	3
Argentina	1	Thailand	1
Brazil	3		
Canada	3	Europe	52
Chile	2	Austria	—
Colombia	—	Belgium	4
Mexico	4	Denmark	1
Peru	1	Finland	6
Uruguay	0	France	6
Venezuela	—	Germany, Fed. Rep.	1
		Greece	1
Africa	7	Iceland	3
Egypt	1	Ireland	3
Nigeria	4	Italy	3
South Africa	—	Netherlands	2
Sudan	1	Norway	5
Tanzania	1	Poland	2
Zimbabwe	—	Spain	5
		Sweden	6
Asia & Far East	20	Switzerland	3
Australia	4	United Kingdom	2
Hong Kong	—	Yugoslavia	1
India	4		
Japan	6	Middle East	3
Korea	1	Israel	3
New Zealand	1	Lebanon	0
Singapore	—		

During the past year the following program changes were made:

●A tentative decision was made that all fellowships would be awarded for only 1 year. This will allow more scientists to take advantage of the program. However, with good justification, fellowships may be extended for up to 6 months.

●In FY 1981, three National Nominating Committees were activated. These were in Romania, Venezuela, and Zimbabwe. The People's Republic of China plans to establish a committee.

●The receipt date for application was changed from December 1 to September 1.

Some FY 1981 IFRP projects of particular interest are:

●Mapping rat brain for antihistamine and B-adrenergic receptors using a new method of studying the bindings of ligands to neurotransmitters and drug receptors in the brain.

●Studying optimal methods for storing platelet concentrates by looking at platelet senescence, types of cells in platelet concentrates that survive the procedures for separating platelets from whole blood, and protection during the isolation procedure.

●Studying molecular basis of liver injury specifically as it relates to derangement in albumin synthesis.

The International Tropical Diseases Research Fellowships

The FIC in cooperation with the National Institute of Allergy and Infectious Diseases and with the United Nations Development Program (UNDP)/World Bank/WHO Special Program for Research and Training in Tropical Diseases has established a program for a limited number of postdoctoral fellowships for training in tropical diseases. Candidates for these fellowships are from countries in which these diseases are endemic: malaria, schistosomiasis, leishmaniasis, trypanosomiasis, filariasis, and leprosy. No awards were made in FY 1981.

International Neurosciences Fellowships

The International Neurosciences Fellowships Program was established in 1977 in cooperation with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the World Health Organization. It is administered by the FIC with funds provided by NINCDS. There were two active fellows during FY 1980, but no new awards were made.

Senior International Fellowships

The Senior International Fellowship Program (SIFP) provides opportunities for established biomedical or behavioral researchers to do collaborative research in a foreign institution. The Senior International Fellowship serves to enhance the exchange of ideas and information about the latest advances in specific areas of medicine, both basic and clinical. It also leads to improvement in the research, education, and clinical potential of the U.S. nominating institution, which profits from the fellows' experience abroad.

During FY 1981, U.S. institutions nominated 114 scientists for the fellowship program. Of this number,

27 percent were funded. The table below lists the host countries which received SIFP fellows.

1981 Senior International Fellowship Awards by Country of Destination

Americas	1	Middle East	1
Peru	1	Israel	1
Africa	0	Europe	27
Asia & Far East	2	United Kingdom	16
Japan	1	France	3
Australia	1	Switzerland	3
		Sweden	1
		Belgium	1
		Germany, Fed. Rep.	3

The SIFP is marked by mutually beneficial collaboration. Some examples are:

- Development of a method to quantitatively analyze Doppler ultrasound spectra patterns to help assess more accurately vessel wall changes, flow disturbances, and flow lesions in the carotid system. This technique is especially useful in the retina, where an invasive technique poses a great risk to the patient.
- Exchange of methods for studying organization of genes and a DNA hybridization technique for knowledge on biology of trypanosomes. This work may be applicable to influenza viruses and make possible the development of an effective vaccine.

Special Emphasis Senior International Fellowship Programs

These programs have the same purpose and eligibility criteria as the Senior International Fellowship Program. Since these programs are administered by the FIC in cooperation with the National Institute on Aging, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, and the National Institute of Neurological and Communicative Disorders and Stroke, the emphasis is on aging, arthritis, diabetes, and epilepsy. For 1981, one award was made by NIADDK for work in arthritis in Australia.

Foreign Government Fellowships

Currently three countries provide fellowships for U.S. scientists to conduct research abroad: Sweden, Switzerland, and France. These are sponsored, respectively, by the Swedish Medical Research Council, the National Science Foundation of Switzerland, and the French National Institute of Health and Medical Research (INSERM). The FIC publicizes the program, advises prospective applicants about the program, reviews the applications for document compliance, monitors the review proceedings, and forwards the applications and summary statements to the appropriate awarding agency. The foreign country agency makes its own funding decision, independent of FIC. In FY 1981, Sweden awarded three fellowships, and Switzerland awarded four. The INSERM program is in its initial phase and made no awards.

Individual Health Scientist Exchange Programs

The Fogarty International Center, on behalf of the Public Health Service, administers Individual Health Scientist Exchange Programs with France, Poland, Romania, U.S.S.R., and Yugoslavia. These programs are components of broader intergovernmental bilateral agreements for cooperation in science and technology, including health, and serve the broad range of health interests of the PHS and the respective foreign ministries of health. They provide mutual opportunities for health professionals to become personally familiar with various aspects of public health and biomedical research activities of the participating host country. By providing support for short- and long-term exchanges, the programs encourage and facilitate direct collaboration and communication between health and biomedical communities of the United States and the participating countries. Through the promotion of person-to-person relationships, the basic goal of the exchange programs is to expand and disseminate scientific knowledge and to foster scientific growth.

- Under these programs, during FY 1981, one American scientist visited Poland to study that country's health policies, planning, and programs relevant to mental health aspects of primary health care, as part of an overall comparative study. Six Polish scientists visited the United States for training in the fields of vascular and abdominal surgery, surgical treatment of ischemic heart disease, thrombosis research, electron microscopy of the haemic cells, hearing impairments, and kidney transplants.

- Seven American scientists visited Romania to conduct a joint workshop on immunology, and one Romanian scientist visited the NIH to discuss future collaboration in cancer research.

- One American scientist visited the Soviet Union to continue his work on the preparation of a biography on Nikolai A. Semashko, the architect and founder of the Soviet health care system; and 10 Soviet scientists, interested in such diverse areas as organ and tissue transplants, pain management in dentistry, lysosomes, hearing aids, coronary surgery, and viral infections, visited a number of research institutions in the United States.

- Four scientists from Yugoslavia received training in radiology, pediatrics, and orthopedic surgery.

Under an agreement between the NIH and the French National Center for Scientific Research (Centre National de Recherche Scientifique), the two organizations share in the support of U.S. scientists selected to work at U.S. laboratories for periods of generally 6-12 months. The type of activity undertaken with a host laboratory may include the conduct of basic or clinical research, familiarization with or utilization of special techniques and equipment not otherwise available, and/or related cooperative efforts. Scientists supported under this program are expected to achieve specific and substantive goals. Seventy-five person-months of work are supported annually by each side. During FY 1981, 10 U.S. scientists worked in French laboratories, and 12 French scientists worked in U.S. laboratories.

NIH Foreign Scientists Assistance Programs

NIH Visiting Program

Foreign scientists have the opportunity to work with NIH scientists in their laboratories under the NIH Visiting Program. FIC provides administrative services to support these scientific exchanges on behalf of the various Institutes. The fellowships provided under this program are funded by the respective Institutes. Administrative support is also provided by FIC for three non-NIH organizations: the Bureau of Biologics of the Food and Drug Administration, the National Institute of Mental Health, and the National Institute on Alcohol Abuse and Alcoholism of the Mental Health Administration. Program participants must be invited by a senior intramural investigator (who will sponsor the visitor's research), and must hold a doctoral degree or the equivalent and have postdoctoral research experience.

The three types of visiting program participants are:

- Visiting Fellows, who have not had more than 3 years' postdoctoral research experience, must be foreign nationals, and receive a 1-year award which is renewable for 2 years.
- Visiting Associates, who have 3 to 6 years' postdoctoral research experience.
- Visiting Scientists, who have more than 6 years' postdoctoral research experience.

Visiting Associates and Scientists are appointed as temporary NIH employees for 12-13 months; their appointments may be renewed for up to 3 additional years. Foreign appointees are subject to visa restrictions. The appointment of a U.S. citizen may be requested only on limited occasions when a Civil Service, Staff or Senior Staff Fellow, or Commissioned Corps appointment is not feasible and subsequent conversion to a permanent appointment is not anticipated.

Distribution of Visiting Program Participants from Top 10 Countries FY 1981

Foreign Countries	No. of Participants	U.S. \$
Japan	183	\$2,552,000
India	126	2,000,000
Israel	69	1,185,000
United Kingdom	73	1,159,000
Italy	74	1,039,000
Canada	35	529,000
Sweden	26	526,000
Australia	28	319,000
Germany	18	300,000
Switzerland	19	299,000

The total Visiting Program participation for all Institutes and NIMH, NIAAA, and BOB in FY 1981 was 1,059 individuals, including 16 U.S. citizens; 155 resident aliens, refugees, and stateless persons; and 888 foreign scientists from 50 countries. There were 707

Visiting Fellows, 192 Visiting Associates, and 157 Visiting Scientists at a cost of \$15.8 million of intramural research funds. This is an increase of 66 individuals over the FY 1980 total of 993 and an increase in total funding of \$2.3 million. The distribution of countries with the greatest activity is shown below.

NIH Foreign Guest Researchers Program

NIH also makes research and study facilities available to qualified scientists who are supported by home institutions and foreign and domestic foundations. NIH has invited Guest Researchers to use intramural facilities since the 1930's; FIC has been responsible for foreign participants since 1968.

In addition to administering the NIH Visiting Program, the Foreign Scientists Assistance Office (FSAO) provides a limited advisory service to other foreign scientists at NIH, particularly in immigration matters. In FY 1981, the FSAO assisted 457 additional foreign scientists. Seventy-seven percent were Guest Researchers funded by sources within their home countries; 9.5 percent were experts funded by the Institutes; and 13 percent were scientists on bilateral agreements, FIC International Research Fellows located at NIH, and Fogarty Scholars. These scientists represented the following geographic areas:

	Guest Researchers	Special Experts	All Others
Europe	187	24	36
Africa	8	—	2
Middle East	15	2	6
Asia and the Far East	101	2	7
Latin America	24	4	3
North America	(Canada) 20	(Canada) 1	(Canada, 6 5 U.S.)

Special Foreign Currency and Joint Funds Programs

The Special Foreign Currency (SFCP) and the Joint Funds Programs are unique resources which enable NIH to engage in international collaborative research and information exchange with biomedical researchers of selected countries for the purpose of investigating health problems of mutual interest and importance. The collaborative character of the NIH program requires that a scientist from an intramural NIH program or from a U.S. academic institution participate in a research project. The participating scientists from both countries select the problem and develop the experimental design. The proposal is submitted to NIH through a coordinating agency in the foreign country for assessment of technical merit by the NIH peer review system.

The SFCP is funded in those countries with currencies designated annually by the Department of Treasury and Office of Management and Budget as excess to the needs of the United States during the subsequent 2 years. The excess currency countries during FY 1981 were Burma, Guinea, India, and Pakistan.

When it has become apparent that funds would be depleted and a country would be removed by the Treasury Department from the excess currency list, the

State Department has negotiated various types of agreements and joint funds, to which each country has contributed equally. To maintain the scientific contacts established under the SFCP, these agreements provide for the use of the residues of U.S.-owned local currencies to establish scientist-to-scientist exchange programs. The agreements also endorse the establishment of institute-to-institute agreements between U.S. academic and research institutions for foreign institutions, which must be funded by the institutions themselves. Countries which have established agreements or joint funds are Poland and Yugoslavia. Activity in the SFCP and Joint Funds Program for FY 1981 is shown below.

One project being funded under the SFCP is a genetics unit consisting of laboratory clinics and a counseling center in Cairo, Egypt, where there is a high prevalence of congenital and metabolic abnormalities and chromosomal defects resulting from traditional marriage practices. This laboratory was the first to describe certain chromosomal defects subsequently confirmed elsewhere. It has provided the basis for advocating measures to reduce the potential for birth defects in the population as well as in individual families. It has also provided U.S. scientists with a source of clinical material such as that for the study of xeroderma pigmentosa, a rare genetic skin disorder in which mental retardation and neurological disturbances occur and in which extreme sensitivity to sunlight produces loss of skin pigment, scarring, and severe skin cancers. Studies of individual cells reveal that there are gene products missing which prevent the ultraviolet damage of DNA.

Country	Number of Applications		
	Submitted	Funded	Continuations
SFCP Funds			
Egypt	14	10	1
	8	4	1
Joint Funds Program			
Poland	3*	0	
Yugoslavia	14	1**	

* awaiting review

** (5) appropriation and deposits

International Coordination and Liaison Program

The International Coordination and Liaison Program (ICLP) serves the key role of coordinating NIH international relationships to facilitate the interaction of scientists and to assist in the exchange of scientific information. It has a liaison responsibility for facilitating communications between NIH and other international offices or agencies. It provides policy guidance, coordination, and general oversight for the participation of NIH with other U.S. agencies in bilateral cooperative agreements between the U.S. Government and other countries.

Bilateral Agreements

The United States is making major contributions toward

the resolution of a broad spectrum of international health problems through its domestic research and related efforts, its cooperative health relationships with other countries, and its participation in the programs and activities of international organizations, notably the World Health Organization (WHO) and the Pan American Health Organization (PAHO). Formal inter-governmental agreements may take a variety of forms, ranging from those of broad scope for educational, cultural, and scientific exchange to more specific ones in science and technology or the health fields. In some instances, a health agreement may be subsidiary to a broader agreement in science and technology. Less formal technical-level agreements may also exist directly between counterpart institutes for a particular purpose.

The bilateral agreements are formal agreements between the Governments of the United States and other countries for cooperative activities; however, much international cooperation in biomedical research occurs without formal mechanisms. The formal agreements form a basis for cooperation in particular situations and circumstances, such as utilizing special resources or surmounting constraints of different social and political systems.

The International Coordination and Liaison Program coordinates NIH participation in all bilateral agreements which involve NIH components and scientists. There are three types of bilateral agreements:

- Agreements made at the government-to-government level which promote broad science and technology objectives.
- Agreements between department-level agencies which may have general preventive health or health maintenance objectives, and which may be concerned with specific disease issues.
- Agreements between NIH and a foreign counterpart in which specific components of NIH are identified as participating in particular disease or biomedical research areas.

During the last decade, international health research and related activities being conducted by DHHS/PHS, and particularly by the NIH, have increasingly been planned as collaborative efforts and have been instituted through special bilateral arrangements. Since the first formal program was signed with Japan in 1965, more than 20 bilateral health agreements have been signed directly between DHHS officials and officials of foreign ministries of health.

Highlights of Bilateral Agreements in FY 1981

New bilateral relationships continue to emerge:

- In FY 1981, a new health agreement, in which the NIH will play an important role, was signed with Kuwait.
- In followup to the opening of formal science and technology relationships in 1980, the NIH initiated consultation with the Zimbabwe Ministry of Health in 1981 regarding potential cooperative activities in biomedical research fields.
- The NIH and officials from the Israeli Ministry of Health held consultations to implement the U.S.-Israel Health Agreement. U.S. areas of interest for continued or new activities have been identified and are currently

under review by Israel for its reaction and counterproposal.

● Formal implementation of the health agreements with Nigeria and Venezuela are expected in 1982, following discussions that have taken place during 1981. The Nigerian Agreement was signed in September 1981; the Venezuelan Agreement, in January 1980.

At present there are 41 agreements which involve NIH with 26 countries. Major agreements are with China, U.S.S.R., other Eastern European countries, Japan, Egypt, Israel, India, and Nigeria. The NIH participates with the following countries in broad agreements covering science and technology cooperation for which the Department of State or the National Science Foundation serves as the executive agency: Egypt, France, India, Israel, Italy, Japan, Nigeria, Pakistan, Poland, Romania, Spain, U.S.S.R., Venezuela, and Yugoslavia. The NIH occasionally participates in agreements with Argentina, Australia, Brazil, Greece, Kenya, Mexico, Senegal, and Zimbabwe. Although the FIC has a role in the administration of bilateral agreements, the scientific content of the projects supported in foreign countries is selected by the collaborating scientists at the NIH in cooperation with the foreign scientists.

Significant events during FY 1981 were:

● The *Second Joint Health Committee Meeting* was held in Beijing in November 1980 with the *People's Republic of China*. Agreement was reached upon programs for hepatitis B vaccine development in China; major epidemiologic study of cardiovascular disease in selected populations in China; a descriptive study of health care and health services in Shanghai city and a reciprocal study by the Chinese in an analogous county in the U.S. The meeting was preceded by a scientific symposium on epidemiology.

● In October 1980, a *U.S.-Federal Republic of Germany (U.S.-FRG) cancer working group* convened in Bethesda, Maryland, to review a series of proposals for cooperation. As a result of these discussions, the working group developed a joint protocol for a Drug Development and Testing Program for Cancer Therapy. This protocol, which provides for a variety of cooperative and exchange activities, was endorsed in a Memorandum of Understanding signed by representatives of the NCI and the FRG Ministry for Research and Technology (MORT) in September 1981. In April 1981, a delegation of U.S. cardiovascular disease specialists participated in a joint workshop on Multiple Risk Factor Intervention Trials in the FRG and reached agreement on several cooperative activities to be carried out over the next 2 years. In the first of these activities, a U.S.-FRG working meeting was held in Bethesda during September-October 1981, for the purpose of discussing cooperative activities with the German National Health Survey on cardiovascular disease.

● In followup to the *U.S.-Israel Health Agreement* initiated in 1980, NIH and Israeli Ministry of Health officials considered during 1981 on the development of a cooperative program to be implemented in biomedical research under the Agreement. U.S. areas of interest for continued or new activities have been identified and are

currently under review by Israel. It is anticipated that formal agreement will be reached in mid-1982.

● In July 1981, the Seventeenth Meeting of the Joint Committee of the *U.S.-Japan Cooperative Medical Science Program (U.S.-JCMS)* met at the NIH. The committee discussed the reports of scientific progress from the eight joint panels on Cholera, Environmental Mutagenesis and Carcinogenesis, Hepatitis, Leprosy, Malnutrition, Parasitic Diseases, Tuberculosis, and Viral Diseases. The Committee expressed its continued satisfaction with the research progress, program guidelines, future plans, and priorities of each of these panels. The third 5-year report (1975-80) of the U.S.-JCMS became available in September 1980.

● Following a restructuring of the program under the *U.S.-Japan Agreement for Cancer Research*, emphasis was placed on cancer etiology, biology, diagnosis and treatment, and interdisciplinary programs. A conference was held on the etiology and epidemiology of stomach and colon cancer. In the treatment area, cooperation was extended to the development of new anticancer drugs and to cooperative clinical trials in treatment of gastric cancer. There was continuing interaction on immunology and immunotherapy for cancer.

● Under the *Agreement between the U.S. and Japan on Cooperation in Research and Development in Science and Technology* (the so-called *Non-Energy Agreement*), cooperation is presently underway in seven areas: the National Toxicology Program, Alcoholism, Immunization, Laboratory Animal Science, Recombinant DNA, Development of Antivirals, and Cardiovascular Disease (Hypertension). The first joint meeting in the cooperative area for recombinant DNA took place February 4-5, 1981, in Honolulu, Hawaii. The participants exchanged information on guidelines, host-vector systems, and risk assessment.

● In May 1981, a *Memorandum of Agreement* between DHHS and the *Ministry of Health of Kuwait* was signed to establish a formal mechanism through which public health technical assistance could be obtained on a reimbursable basis. No specific areas of interest have been identified as yet.

● Under the *U.S.-Nigeria cooperative agreement in health*, the NIH will have the lead role in the subcommittee program area of biomedical research (multiple Institutes). NIEHS and NIOSH will share responsibility in the area of environmental and occupational health. At the first meeting of the Joint Working Group on Health Cooperation held in Bethesda, Maryland, in February 1981, NIH and Nigerian representatives shared their views on areas of specific interest for cooperation in biomedical research fields.

Subsequently, a preliminary U.S. proposal was submitted to the Nigerian Ministry of Health as a basis for further consideration and refinement, and especially to elicit Nigerian priority interests for incorporation. At the Joint Bilateral Economic Talks in September 1981, the Nigerian health representatives still had the proposal under consideration. In the meantime, longstanding cooperation in several areas continues.

●Under the aegis of the *U.S.-Romania Agreement on exchanges in education, culture, science, and technology*, occasional exchanges in the health fields have taken place, primarily of U.S. specialists visiting counterparts in Romania. The major form of exchange continues to be the holding of joint biomedical research workshops, particularly in fields of cancer research, with the NCI being the principal partner on the U.S. side. After the last workshop in November 1980, in Romania, it was agreed that the next would be in the spring of 1982 in Bethesda, Maryland, on other aspects of cancer research.

●The *Interim Coordinators in biomedical research for the U.S. and Venezuela* have been named. The U.S. Interim Coordinator visited Venezuela in July 1981 to hold discussions on implementation of the Memorandum of Understanding. On the basis of these discussions, the priority areas under consideration for collaboration in biomedical research are leprosy, Chagas' disease, cardiovascular disease, diarrheal disease, and maintenance of scientific equipment. No final decision has been made on these areas yet. Other areas to be explored are technology transfer of hybridoma and recombinant DNA research capacity, research manpower training, and epidemiology/clinical research.

Other Liaison Functions

In addition to monitoring and assisting in bilateral activities, the International Coordination and Liaison Program maintains liaison with WHO and PAHO and occasionally other multilateral organizations, and provides the NIH positions on agenda issues for World Health Assemblies and the PAHO Directing Council meetings. The program provides material for the NIH participation as an observer in the European Medical Research Council meetings. Requests for services of NIH experts for WHO and PAHO committees and other purposes are processed with DHHS through the program.

The program assists the Institutes by reviewing and clearing foreign travel notifications and by serving as a channel for cable communications to and from foreign embassies and the Department of State to NIH, by coordinating responses to inquiries on international issues, and by processing NIH foreign grants and contracts for clearance through the Department of State.

The FIC Director meets periodically with international representatives of the NIH Bureaus, Institutes, and Divisions to exchange information and views on NIH international activities and to discuss implementation of related policies and procedures. The meetings are organized by the program.

The program collects information on NIH international activities and reports on these annually. It frequently prepares special reports about certain countries as background for travel of an NIH principal or a visiting official; it also prepares comprehensive briefing books.

The program serves as project focus for U.S. Government core support for the Gorgas Memorial

Institute of Tropical and Preventive Medicine, Inc., and the Gorgas Memorial Laboratory in Panama provided through the FIC budget.

The program also conducts special studies relevant to its responsibilities. The principal thrust of the special studies in FY 1981 was on collecting information on biomedical research resources and funding in industrialized countries in Western Europe, Australia, and Japan, and on compiling information on biomedical research institutions in the People's Republic of China. The first project was carried out by the Organization for Economic Cooperation and Development (OECD) under partial contract support by FIC. A report has been submitted and is under study. It is expected that this report will be circulated during FY 1982.

The second project will lead to the publication in 1982 of a directory to be used by American scientists and administrators planning to visit China or collaborate with Chinese scientists. It will contain names and locations of the institutions, directors, and laboratory chiefs, and selected recent publications from the institutions.

During FY 1981, two books were published on health care: *Rural Health in the People's Republic of China*, a report by the Committee for Scholarly Communications with the People's Republic of China National Academy of Sciences, and *Universal Free Health Care in Canada, 1947-1977*, by G. Hatcher, Albany Medical College of Union University.

Gorgas Memorial Laboratory, Panama

In 1928, Congress authorized a permanent annual appropriation to the Gorgas Memorial Institute of Tropical and Preventive Medicine, Inc., Washington, D.C., for the operation and maintenance of a research laboratory in Panama. This action, together with land and building donated by the Government of Panama, permitted the establishment of the Gorgas Memorial Laboratory (GML). Since FY 1971, the FIC budget has provided the annual U.S. core support funds, which amount to \$1.8 million in FY 1981. The FIC maintains general program oversight for this funding.

The laboratory conducts a diversified program of research on diseases prevalent in the tropics that are of importance to the United States, Panama, and the region. Particular emphasis is placed on virology, parasitology, and the effects of environmental change on disease vectors and transmission. In addition to conducting research, the laboratory makes its facilities available for visiting scientists and the training of professional personnel. It has cooperative arrangements with several U.S. universities for graduate and medical student body and course credit. Formal training courses in tropical medicine are conducted several times a year for U.S. Navy medical officers.

For FY 1981, the Gorgas Memorial Laboratory had a number of substantial scientific accomplishments to report. Collaborative programs with the Yale Arbovirus Research Unit (YARU), the U.S. Army Medical Research and Development Command, the Ministry of Health of Panama, the Panamanian National Oncology

Institute, and the Centro Regional Universitario de David were continued. Specific activities for the year were in the following areas:

- Acute hemorrhagic conjunctivitis (AHC)*: In cooperation with the Ministry of Health of Panama, GML provided virologic and serologic diagnosis and conducted a detailed seroepidemiologic survey for this disease, which caused an epidemic in Panama this year.

- Yellow fever*: In cooperative research with YARU, vector mosquitoes were found to have substantial individual variation in their ability to produce, and, presumably, transmit, yellow fever virus.

- Cancer registry*: In cooperation with the Panamanian National Oncology Institute, GML has maintained the Panamanian National Cancer Registry since 1977.

- Cervical cancer*: As part of a detailed standardized Cervical Cancer Registry (which supplements the National Cancer Registry mentioned above), GML examined all discharge diagnoses, all hospital death records, and all operating room logs dated 1974 to 1980, from all hospitals in Panama City, Colon, Chiriqui, and Herrera Provinces, to ascertain all cervical cancer patients. A review of the hospital charts for all such cancer patients, beginning in 1974, was completed through 1979, with 1980 underway. A direct case-control study in Herrera Province has begun since data showed a high rate to be associated with birth in that province.

- Sexually transmitted disease (STD)*: The GML STD program, in cooperation with the Ministry of Health, includes the newer recognized STD's as well as gonorrhea and syphilis. As part of this program, unique to Central America, GML in 1981 completed

epidemiologic and sexual history interviews of 400 workers, with blood samples from all, and endocervical cultures from 250.

- Sandfly fevers*: During 1980, infection with both Punta Toro virus and Chagres virus were demonstrated in a sample of some 2,000 sera drawn from U.S. military personnel in Panama.

- Environmental assessment*: As part of the environmental assessment project supporting the Tabasara hydroelectric project, GML completed a health status survey of over 4,000 residents of this remote area.

- Diarrhea*: This year a study was conducted comparing children hospitalized for diarrhea with unhospitalized rural children. In this pilot study, 1 percent of rural children harbored the pathogen for diarrheal disease (*Campylobacter fetus jejune*), while 12 percent of children with diarrhea were positive.

- Diphtheria*: Forty-seven Panamanian medical students and 30 rural inhabitants were Schick-tested for diphtheria susceptibility. All rural inhabitants (ranging from 13 to 64 years of age), but only 60 percent of the students (ages 19 to 23) were found to be immune.

- Training*: The course "Medicine in the Tropics," presented jointly with the U.S. Naval Medical Research and Training Unit located at GML, was given three times during FY 1981 to a total of 25 military medical officers, two students from the Uniformed Services University of the Health Sciences (USUHS), and one civilian medical student. The course was expanded to include a 3-day session on jungle survival.

A complete annual report of the GML is prepared each year for the Congress.

NATIONAL CANCER INSTITUTE

Introduction

The prevention and control of cancer depends upon knowledge of causation, identification of population risk groups, availability of early detection measures, and the means for effective intervention. Throughout the world marked differences exist in the environmental, occupational, and social conditions of people. Such factors are believed to significantly influence the incidence and course of many, if not most, types of cancer. Thus, the efforts of world specialists engaged in cancer research are stimulated and enhanced through international interaction, by collaborative studies, and by the exchange of scientific results. Through its participation in the international cancer scientific community, the National Cancer Institute (NCI) ultimately benefits from the rapid advances in basic research throughout the world and their application to the clinical management, control, and prevention of cancer. The ultimate gain from such collaborative cancer research efforts between the NCI and international counterparts is a tangible improvement in the quantity and quality of health services to millions of people the world over.

The contribution of NCI to the international struggle against cancer includes: (1) the continuing support of cancer research in foreign countries by highly qualified scientists; (2) the support of cooperative research programs, principally under bilateral agreements with foreign governments, institutions, or organizations; (3) the maintenance of liaison and research collaboration with international organizations and agencies that have well-defined objectives in cancer research and cancer prevention; (4) the support of training of foreign scientists in the United States as well as of the interaction of American scientists with colleagues in foreign laboratories; and (5) the management and operation of an International Cancer Research Data Bank for promoting and facilitating, on a world-wide basis, the exchange of information for cancer research, care and management of patients, and cancer control and/or prevention.

Summary of Programs Activities: Bilateral Agreements and Other Country-to-Country Activities

Cooperative cancer research programs under formal

government-to-government treaties and other forms of bilateral agreements make up a major segment of the international activities of the National Cancer Institute. The first of these cooperative cancer research agreements was established on May 23, 1972, with the signing of the U.S.A.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health. Subsequently, additional bilateral programs were formalized between the NCI and the Japanese Society for the Promotion of Science (1974); the Institute of Oncology, Warsaw, Poland (1974), under the U.S.A.-Polish People's Republic Agreement; in 1975, with the French Institut National de la Santé et de la Recherche Médicale (INSERM) under an earlier NIH Agreement with INSERM; the Cairo Cancer Institute (1976), under the aegis of the agreement between the U.S.A. and the Arab Republic of Egypt; the Ministry of Science and Technology of the Federal Republic of Germany (1976); the Cancer Institute (Hospital), Chinese Academy of Medical Sciences, under the U.S.A.-People's Republic of China Accord for Cooperation in Science and Technology (1979); the National Cancer Institute of Milan and the Institute of Oncology of Genoa, Italian Republic (1980); and the National Institute of Oncology, Budapest, Hungary (1981).

Egypt

The effort between the NCI and the National Cancer Institute of Cairo University continued under the Special Foreign Currency Program (P.L. 480). Three ongoing programs include the treatment of bladder cancer, cytopathology of bladder cancer, and cooperative clinical studies, under the Southwest Oncology Group (SWOG), for the treatment of breast cancer, head and neck cancers, adult lymphomas, and childhood lymphoma.

In 1981, the results were published on a joint American-Egyptian study, initiated in Egypt in 1976, for the evaluation of urinary cytology as a screening method for the early detection of bladder cancer in a rural community where the parasitic disease, schistosomiasis, is endemic. Additional goals included the identification of a high-risk group related to schistosome infestation and the determination of the prevalence of urinary bladder carcinoma and its precancerous lesions in that population. In this study, the definition of the high-risk group proved to be valid since all tumors were detected among farmers in the high-risk

group; and, no tumors were detected among the control groups of the rural population. In farmers who work daily in the field, the schistosomal infestation, with frequent reinfection, is most intense. Nonfarming villagers, living in the same rural community, get milder forms of infestation often related to accidental contact during swimming or washing. This is considered to be epidemiologic evidence of the relationship between schistosomiasis and urinary bladder cancer.

Urine cytology, in this experience, proved to be an effective method for population screening. The yield of the screening was 11 cases of histologically confirmed carcinomas among 8,744 individuals screened. All 11 cases were in the high-risk group; none were detected in the two low-risk control groups. A yield of two per 1,000 of high-risk was obtained. This would also constitute a 4/10,000 of all rural population. And, knowing that about half of the population is below the age of 20, the prevalence rate could be estimated as 8/10,000 of the rural adult population.

Thus, the American and Egyptian scientists successfully concluded a joint project and demonstrated that a screening program is productive, if conducted in and restricted to high-risk groups. It is especially true in view of the limited funds, manpower, and medical facilities.

Federal Republic of Germany

An NCI delegation met in Heidelberg in April 1980 with a German delegation representing the German Ministry of Research and Technology and the German Cancer Research Center (DKFZ), to discuss formalization of bilateral cooperation on Environmental Carcinogenesis. A Memorandum of Understanding was signed by the Director, NCI, and the Director, DKFZ, in February 1981, for cooperative research on: the causation and mechanisms for carcinogenesis and the prevention and modulation of the carcinogenic process.

In October 1980, a German delegation met with members of the NCI staff to discuss possibilities of cooperation in the areas of drug development and clinical studies. In addition to personnel and information exchanges, collaboration efforts are directed toward broadening the spectrum of tumor screening, beyond existing American and German models currently in use. This program is designed especially for the development of alkylating cytostatics. Human tumor xenografts are to be used for pharmacologic characterization of new cytostatic agents.

Another area of joint research relates to the synthesis and development of stabilized, "activated" oxazaphosphorine analogs (e.g., cyclophosphamide) with high toxic specificity and cancerotoxic selectivity, which can be used in local regional chemotherapy. The development of stabilized oxazaphosphorine analogs is of special interest for the improvement of systemic chemotherapy, especially where the goal is the selective destruction of tumor cells in conjunction with the transplantation of autologous bone marrow. There will be joint research on regional detoxification of anticancer drugs from the point of view of optimal detoxification of the drug for the benefit of normal tissues with

simultaneous improvement in tumor chemotherapeutic efficacy.

France

In Paris, in December 1979, NCI agreed in principle to a French proposal for the reorganization of the American-French Program and combined the former Viral Oncology and Hormone/Cancer Working Programs into one which would be dedicated to Basic Research in Carcinogenesis. The other program deals with Clinical Cancer Research.

The Clinical Cancer Research Program encompasses the activities which were included formerly under the Clinical Trials and Treatment Research Program. However, the scope has been expanded to include immunotherapy, hormone therapy, and studies on hormone receptors. Thus, the American-French clinical research effort includes: Phase I and II clinical trials and preclinical studies of the efficacy of anticancer drugs such as nitrosoureas, anthracyclines, and platinum analogs; Phase III studies of gastrointestinal tumors; and the treatment of resistant breast cancer. Other collaborative efforts are devoted to the study of multiple pharmacologic and biochemical determinants.

The program in Basic Research in Carcinogenesis is considered to be one of broad spectrum wherein meritorious scientific studies of a nonclinical nature are to be undertaken. These include such areas as cell proliferation, cell growth factors, normal and cancer cell differentiation, molecular genetics, tumor promoters, DNA repair, induction of cell transformation by DNA and RNA viruses, chemical and physical carcinogenesis, etc.

In October 1980, the Joint U.S.-French Committee on Basic Cancer Research met in Paris to review the activities of the past year and to plan for exchanges of scientists for fiscal year 1981. During the first 4 years of cooperation, 36 French scientists visited and studied in American laboratories, while 35 American investigators spent varying periods of time working in French laboratories. These collaborative efforts resulted in more than 35 joint publications.

In view of increasing costs of travel and research expenses, the joint committee agreed that selection of exchange scientists will be based on the highest scientific merits and relevance to the goals of the cooperative program for mutual benefit. During the meeting, the French committee reported that 12 research grants were made by the National Institute of Health and Medical Research (INSERM) to support cancer projects for collaborative research between American and French investigators. It was agreed that bilateral relationships would be very productive and elicit new avenues of research. The joint committee stressed the importance of the exchange of scientists to engage in collaborative research activities, to exchange techniques and research ideas, and to develop approaches to engender continuous interaction and cooperation. During the year, seven French scientists spent varying periods of time (a few weeks to 12 months) in American laboratories, while seven American investigators worked in French laboratories en-

gaged in basic research, particularly in molecular biology, biologic carcinogenesis, and hormone research related to cancer.

The Joint NCI-INSERM Committee on Cancer Clinical Research met in Bethesda in December 1980 to review and evaluate the collaborative activities of the previous year. The meeting was cochaired by the Director, NCI, and a representative from INSERM. The discussion centered on the ongoing activities in clinical studies and treatment research. The joint committee agreed that the program area should be expanded to take advantage of unique developments that might arise in treatment research. This can be accomplished through the use of workshops to exchange ideas and clinical and experimental data, as well as scientist-to-scientist exchanges.

The French committee reported that the committee was expanded to include other disciplines, such as epidemiology and radiation therapy, in order to cover areas which were not previously included. During the year, the French committee reviewed and selected proposals leading to 18 research grants for the support of collaborative research between American and French scientists.

The joint committee agreed to form several working groups: Working Groups for Clinical Trials; Clinical Biochemical Pharmacology; Biologic Response Modifiers; Radiation Therapy; and Epidemiology. These would meet to discuss areas of mutual interest for future collaborative efforts. There was general consensus to continue collaboration on the treatment of gastrointestinal cancers; clinical trials; pediatric oncology; new drug development; exchange of scientists for collaboration in clinical biochemical pharmacology; exchange of information in radiation therapy, including hyperthermia, radiosensitizers, labeled antibody, and time-dose delivery; and the exchange and coordination of information in the epidemiology study of nasopharyngeal cancer and high-risk cancer.

During the year, three American cancer specialists and four French investigators were appointed as exchange scientists to engage in collaborative research.

In February 1981, a French scientist was invited to attend the NCI-sponsored meeting on "Hybridoma Research," which was held at NCI. Also, two French investigators attended a "Workshop on T cells," held in Bethesda in June 1981. Several French oncologists also attended the annual meetings of the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO), which were held in Washington, D.C., in April 1981.

Hungary

A delegation of Hungarian cancer researchers visiting the United States in December 1978, and Americans visiting Hungary in June 1979, exchanged proposals for initiation of joint research between scientists of the two nations. Subsequently, on February 23, 1981, a Memorandum of Understanding for a Cooperative Cancer Program was signed by the Director, NCI, and the Director, National Institute of Oncology, Budapest, Hungary. Priorities for scientific activity are given to

studies in the areas of: Cancer Epidemiology/Etiology; Experimental Pathology; Immunology with emphasis on the Leukemias and Hematologic Research; and Cancer Therapy and Developmental Therapeutics.

Implementation of activities under this agreement followed in September 1981, as two American immunologists journeyed to Budapest, and the NCI received three Hungarian specialists, each for 6 months.

The American immunologists devoted their time to exchanges of information on: conditions under which receptors for immune globulins are shed from the cell surface and the nature, structure, and function of the shed receptors vis-a-vis those that are bound to the cell surface; natural killer (NK) cell activity in normal human donors and NK activity in patients with various types of cancer, especially breast and lung cancers; analyses of NK cytotoxicity and its possible utility for determining the prognosis in cancer patients; the production of high levels of alpha and gamma interferon from human peripheral blood leukocytes; and the production of a wide variety of monoclonal antibodies. They participated, as well, in a meeting on "Signal and Signal Processing in the Immune System."

One of the Hungarian visitors, an experimental chemotherapist, is spending her time with colleagues at the NCI engaging in studies designed to investigate the resistance of murine tumor cells to alkylating agents utilized as anticancer drugs. Her work thus far has confirmed the role of glutathione, a tripeptide, in resistance to alkylating agents. She is now completing in vitro studies with buthionine sulfoximine, which is an inhibitor of glutathione biosynthesis. These studies have demonstrated that it is possible to completely sensitize the resistant cell to the cytotoxic effects of an anticancer drug such as L-phenylalanine mustard (L-PAM). L-PAM is one of the effective drugs, used in combination with others, for the treatment of breast cancer.

The transplantation biologist/tumor immunologist from Hungary is spending his initial 4 months in the Sidney Farber Cancer Institute. His efforts are devoted to joint research on developing in endothelial cells monoclonal antibodies active against T cells and monocytes. His approach is to collect endothelial cells from the umbilical cord and collect the antigens acting against the monoclonal antibodies. At the same time, he is learning techniques for the separation of lymphocyte subcell populations and the differentiation of chronic myelocytic leukemia cells under conditions of a variety of stimuli.

The third Hungarian scientist, an experimental pathologist/chemotherapist, took to Roswell Park Memorial Institute four human colorectal tumors transplanted in xenographic mice. He is using these and tumors obtained from RPMI patients to study methods of disaggregation—mechanical and enzymatic—to yield single-cell suspensions. At the same time, he is developing cell separation methodologies for biochemical, biologic, and morphologic characterization of the various tumor subsets derived from the human cell suspensions. The subsets, then, are tested for their sensitivity to anticancer drugs. Thus, this segment of

American-Hungarian collaboration is considered to be mutually beneficial and constitutes a significant contribution to the clinical biochemical pharmacology programs ongoing in both countries.

Italy

Following upon the agreement reached in early 1980 for the pursuit of joint studies in Cancer Therapeutics and Cancer Prevention, a number of joint projects have been undertaken that have yielded some mutually beneficial results.

In the Cancer Therapeutics area, an American-Italian workshop on "Clinical Biochemical Pharmacology" took place in Milan in November 1980. The objective of the session was to focus on opportunities for collaborative studies on, for instance, the heterogeneity of cancer disease and the need for individualized treatments determined according to the characteristics of each case. Another point of exchange was the relationship on cell sensitivity or resistance to an anticancer drug and the capacity of the cell to repair the DNA damage caused by the drug. An approach considered was the means for enhancing the binding of an anticancer drug, such as chlorozotocin, to the chromatin of the cell nucleus by steroids such as hydrocortisone. The latter was considered in light of a potential synergism of action between anticancer drugs acting as alkylating agents and the corticosteroids.

Thereafter, cooperative relationships for joint therapeutic projects were established for studies on the treatment of breast cancer, Stages I-III, using new combinations of chemotherapy as well as the combined modalities approach; on the treatment of pain, nausea, and anorexia in pediatric cancer patients; on the biochemical-pharmacologic parameters of drug action; on new chemical analogs of Adriamycin and daunorubicin, which appear in preclinical tests to offer advantages in terms of efficacy of treatment and reduced cardiotoxicity in a broader spectrum of tumors; on biologic response modification, including use of thymic factors, interferons, monoclonal antibodies, and immunomodulation in a variety of immunity model systems; and on experimental metastases models, especially those related to membrane metabolism and cellular control of neoplastic growth.

In the Cancer Prevention area, the U.S.-Italy Joint Committee met in Bethesda, in November 1980, to discuss areas for cooperative research, including: cancer epidemiology; chemical carcinogenesis; detection and diagnosis; and biologic carcinogenesis. The mechanisms for implementation involve an exchange of scientists; an exchange of information and research resources; and the design and development of joint research projects.

Currently, an Italian biologist is engaged in joint research in the Center for Experimental Biology, The Mount Sinai Medical Center. He is studying the relationship between polyamine synthesis and differentiation in an attempt to elucidate the biologic role of these compounds in the steps leading to differentiation of erythroleukemia cells in a model system developed at Mount Sinai. Polyamine biosynthetic enzymes appear to be involved in the differentiation of

these cells. Thus, he is investigating the mechanisms of action of two enzymes, hoping to determine whether the appearance of specific biochemical markers of differentiation correlate with polyamine biosynthesis. These studies could shed some light on the cause of a "block in maturation" of malignant cells.

An Italian epidemiologist spent 3 months in NCI working in the field of occupational epidemiology.

And, at the Fox Chase Cancer Center, a young Italian physician is participating in the joint study of the interrelations of hepatitis B infection, iron metabolism, and primary hepatocellular carcinoma. Her contribution to this project is clinical information and serum samples from parents and siblings of 125 Italian children who have thalassemia. Children with thalassemia, predictably, are at increased risk of becoming chronic carriers of hepatitis B virus and, hence, at increased risk of developing primary hepatocellular carcinoma.

Japan

In May 1979, the Joint American-Japanese Steering Committee restructured this cooperative cancer program to provide greater flexibility and breadth in order to accommodate current changes in the fields of cancer research. For the next 5-year period, the 11 research specialties being pursued jointly were categorized in four broad program areas: Etiology, Cancer Biology and Diagnosis, Cancer Treatment, and Interdisciplinary Research.

The major objectives of the Etiology Program Area are to identify carcinogenic factors and to elucidate the mechanisms of carcinogenesis in an attempt to provide fundamental bases for understanding the cause of human cancer. This program includes four closely related subareas: epidemiology, chemical carcinogenesis, viral carcinogenesis, and genetics.

During this reporting period, key American-Japanese activities focused on scientific exchanges in the areas of biochemical epidemiology and chemical carcinogenesis. From discussions on the role of dietary factors in cancer causation, the need was established for new laboratory assays that might detect specific dietary constituents or metabolites in the urine, feces, or other body fluids. The basis for this determination is the questionable reliability of dietary histories and the need for identification of specific components of the diet.

The recent discovery of the Japanese that "highly potent" mutagens can be formed during the broiling of fish provides a striking example of carcinogens associated with nutritional habits. Discussions on the complexities of carcinogen metabolism highlighted the need for further assessing individual variation in humans.

The development of antibodies to specific carcinogen-DNA adducts was highlighted as a potentially useful tool in the detection of human cancers through tissue sample analyses, providing a "dosimeter" of carcinogen exposure and metabolism. Highly sensitive methods of mass spectrometry and of combined liquid chromatography-mass spectrometry were reviewed from the viewpoint of being utilized to detect extremely small amounts of carcinogens in environmental samples and body fluids (i.e., breast fluid or semen).

Epidemiologic and clinical findings related to T cell lymphomas were reviewed. The lymphomas appear to occur in clusters of high incidence in certain prefectures in Japan. It was interesting to learn that these cases show an abnormality of chromosome 14. Possible contributing factors include a mosquito-borne virus and a species of filaria.

Discussions on tumor production revealed direct effects of saccharine on *Concanavalin A* agglutinability of rat bladder mucosal cells; the discovery of a specific membrane-associated receptor for the phorbol ester tumor promoters; and the discovery of a new, "highly potent" class of tumor promoters, teleocidin and Lyngbyatoxin, that are naturally occurring indole alkaloids. Lyngbyatoxin was found in edible seaweed. Teleocidin is a compound that has been isolated from *Streptomyces*. Both of these promoters demonstrate biologic activity against mouse skin and cell membrane receptor(s).

During fiscal year 1981, two American and six Japanese investigators were appointed as Exchange Scientists in the Etiology Program Area. The scientists presented seminars and engaged in collaborative research activities in the areas of chemical and biologic carcinogenesis, molecular genetics, and epidemiology.

Under the Cancer Biology and Diagnosis Program Area, a meeting was convened in October 1980, in Osaka, Japan, on "Immunology: Biology, Genetics, and Preclinical Immunotherapy." Seven American and more than 10 Japanese participants presented papers, providing significant advances in this area of interchange. Within the field of basic immunology of host-tumor interaction, the topics of discussion included: the existence of tumor-specific antigens; the role of regulatory events in determination of host immune response to tumor; and the roles of cytotoxic T lymphocytes, macrophages, and natural killer cells as effectors of antitumor responses. Preclinical studies in experimental immunotherapy were also presented and dealt with areas of both tumor prophylaxis and active therapy.

A conference on "Oncodevelopmental Proteins: Basic Biologic and Clinical Aspects" took place in San Diego, California, in December 1980. The information generated during this exchange between American and Japanese specialists is considered to be significant in advancing the state of the art in cancer immunology. Some of the highlights relate to Japanese experiences with horse antibodies (HA) to human or rat alpha fetoprotein (AFP). Although the HA's exhibit apparent cytotoxic effects on cultured hepatoma cells and transplanted rat hepatoma, only slight effects were observed in tests with human hepatoma or testicular tumors in nude mice. Japanese studies of the mechanism of AFP gene expression revealed that AFP synthesis is controlled at transcription with no indication, thus far, of the AFP gene during ontogenesis and oncogenesis. Japanese scientists described the complexities of the dynamics of AFP in patients with hepatitis, liver cirrhosis, and hepatoma. In hepatoma, 64 percent showed highly elevated AFP values ($>10,000$ ng/ml), whereas in chronic hepatitis, the levels are usually

normal; cirrhosis (33 percent) exhibited modest elevations of serum AFP. Two other observations were presented: administration of pyridoxine and ATP decreased AFP levels in persons with cirrhosis but not hepatoma; and the Con-A nonreactive fraction of AFP is less than 5 percent in patients with hepatoma, in contrast to 40 to 50 percent in patients with metastatic liver cancer. In viewing primary hepatocellular carcinoma, Americans emphasized that: (1) geographic and sociologic differences relate to hepatitis B virus (HBV) status and the natural history of human hepatoma. Screening of susceptibility for hepatoma can now be considered by probing for integrated HBV DNA in patients' liver cells; (2) serum AFP is most useful in cancer detection when the lesion is not clinically obvious; (3) high serum ligandin (GSH transferase) levels appear to correlate with well-differentiated liver cancer, whereas high AFP correlates with less well-differentiated types.

During the January 1981 symposium on "Genetic and Epigenetic Aspects of Cancer," in Honolulu, Hawaii, two general approaches were taken toward understanding the biology of cancer. The first involved the use of animal models to study the relative role of genetic and epigenetic factors in the development of cancer. The second approach involved the use of tissue culture systems to study the molecular basis of transformation by viral agents.

During the year, two American and one Japanese investigators were appointed as exchange scientists under the Cancer Biology and Diagnosis Program Area.

The Cancer Treatment Program Area continued to become progressively more multidisciplinary during the past year, balancing modality-oriented and disease-oriented seminars and exchanges. Radiation oncology continues to be of increasing importance in the exchange, as both countries work in the areas of high LET radiation, radiation sensitizers, radiation protectors, and hyperthermia. The exchange of information between American and Japanese scientists in this area is helping to advance the science more rapidly in both countries and is setting the stage for future collaboration.

Chemotherapy still remains a major focus of the cancer treatment area. The exchange of drugs and data in the preclinical area is vigorous, aiding both countries toward more rapid progress. At the clinical level, a vigorous exchange continues as well. Based on the Japanese experience, clinical studies of Aclacinomycin A have begun in the U.S.A. Clinical studies here will soon begin on PEP-bleomycin, again based on the clinical experience in Japan. Both countries are placing emphasis on new anthracyclines, fluorinated pyrimidines, and nitrosoureas. From a disease-oriented perspective, emphasis is placed on tumors of the lung, breast, gastric area, and bladder. The results of the recently completed collaborative protocol in advanced gastric cancer between the Northern California Oncology Group and Japanese investigators has demonstrated comparability of Japanese and American data in the chemotherapy of this cancer. A second-generation

protocol has been developed and has just been activated.

The "Breast Cancer Treatment Symposium," held in San Antonio, Texas, in March 1981, concentrated on the use of combination chemotherapy and endocrine therapy in the treatment of advanced breast cancer. The increased interest stems from the development of the estrogen receptor assay and of new hormonal approaches to the treatment of breast cancer, particularly the antiestrogen drug tamoxifen. The drug combination therapy approach to breast cancer is now well-established in both countries. It is hoped that combining the two modalities will dramatically improve survival. Chemotherapy data from Japan were presented which correlated with the American data, indicating that the two countries were using drugs in a similar way and achieving comparable results. The data on hormonal assays in both countries demonstrated comparability as well.

Two Americans and one Japanese were appointed as exchange scientists during fiscal year 1981 to share views on recent progress and stimulate further collaboration in the Cancer Treatment Program Area.

In the Interdisciplinary program area, a workshop was convened on "Differences in Lymphocytic Diseases between the U.S. and Japan," in Honolulu, March 11-12, 1981. The meeting was based on the observation that high rates for lymphoproliferative disorders are associated with low rates of autoimmune diseases. Among U.S. whites, lymphoma occurs more frequently in males; autoimmune diseases occur more frequently in females (e.g., systemic lupus erythematosus [SLE] M:F-1:9, and Hashimoto's thyroiditis M:F-1:20). A reciprocal relation between the two categories of disease is also found when data from the U.S. and Japan are compared. Certain lymphoid neoplasms are rare in Japan, and certain autoimmune diseases are known or suspected to occur more frequently in Japanese than in Caucasians. As a result of this meeting, plans were made for several Japanese and American investigators to extend collaborative efforts to compare the frequency of SLE to other relatively common autoimmune diseases; to investigate rare cases of adult T cell leukemia in the U.S.; to study the distribution and determinants of subacute necrotizing lymphadenitis in Hokkaido; and to develop a hypothesis concerning ethnic differences in T cell function to account for the excesses and deficiencies in the lymphocytic diseases.

During the year, a Japanese surgeon spent 6 months at the Memorial Sloan-Kettering Cancer Center to study the recent advances in the diagnosis and treatment of pancreatic cancer, especially the technique for regional pancreatectomy.

People's Republic of China (PRC)

During its meeting on November 19, 1980, in the PRC, the U.S.A.-PRC Joint Committee on Medicine and Public Health approved the joint cancer proposal which is included in Annex 2 to the U.S.A.-PRC Protocol for Cooperation in the Science and Technology of Medicine and Public Health. The American-Chinese cooperative cancer effort thus includes studies of the epidemiology, early detection and diagnosis, treatment, and multidis-

ciplinary studies of esophageal cancer.

In compliance with the provisions of the 1980 cancer accord, the NCI has extended invitations to three Chinese principals for protracted periods of study and joint research in the NCI and other American cancer centers. One is to engage in studies of the use of endoscopy and other diagnostic procedures in cancers of the esophagus and lung. Research on the epidemiology of esophageal cancer and studies of technology for analytic epidemiology constitute the objectives of the second Chinese specialist. The third will pursue a program of study and research in cancer epidemiology and medical statistics.

Under the aegis of the U.S.A.-PRC Protocol and during the interval of September-October 1981, five American scientists visited the People's Republic of China—two for periods of 2 weeks; two each for 4 weeks; and the fifth for a period of 6 weeks. One of these traveled for the purpose of participating in workshops and teaching Chinese colleagues in the methods of organic and medicinal chemistry for the design and development of anticancer drugs, their preclinical testing, and potential utility in treating esophageal and other cancers. In this context, another of the American visitors intended to participate in scientific exchanges, principally in pharmaceutical institutes, on Chinese development of anticancer drugs and use of products of natural origin in the treatment of cancer. The third American was to engage in scientific exchanges on the relationship of dietary selenium to the incidence of esophageal and other cancers. Included in his program were discussions of chemical carcinogenesis and nutritional factors as they may be related to cancer. Early detection of cancer, with particular emphasis on cytogenetic-epidemiologic, as well as pathomorphologic, analyses and technologies, were among the scientific topics to be pursued by the last two American visitors.

Prior to the adoption of the 1980 U.S.A.-PRC collaborative cancer program, a joint NCI-Cancer Institute (Beijing) study was initiated in the area of biochemical epidemiology. The research embodies the collection and cultivation, in China, of human fetal tissues (liver, esophagus, stomach, and bronchi) for use in the identification of biochemical markers that may be associated with cancers of these organ sites. In tissue samples brought to the NCI by the Chinese collaborator, aflatoxin-B₁-DNA adducts have been isolated from liver samples taken from donors in cancer high-risk areas. This was done by use of monoclonal antibodies to aflatoxin B₁, a technique developed by NCI scientists and taught to the Chinese.

Poland

The Agreement for Cooperation in Cancer Research was renewed, in April 1981, for an additional 5 years of collaborating effort between the National Cancer Institute and the Maria Skłodowska Curie Memorial Institute of Oncology. The accord has been a very important addition to the Polish National Cancer Program, in that it provides support for the exchange of information and scientific personnel.

During fiscal year 1981, Exchange Scientists from Poland included a molecular biologist who studied at the NCI; a radiologist who trained at Harvard Medical School; a surgeon who studied the treatment of gastrointestinal cancer at the University Hospital in Cleveland, Ohio; a physiologist at the National Heart, Lung, and Blood Institute; a pathologist who visited several leading American departments of pathology; and a radiotherapist at the University of Texas System Cancer Center. The Head of the Oncology Clinic, National Research Institute of Mother and Child of Warsaw, attended a conference on Pediatric Oncology in Washington, D.C., and later exchanged ideas with NCI staff on possibilities for cooperative research on the treatment of childhood cancers.

An NIH senior scientist visited the Institute of Oncology in Warsaw to consult with the staff in the Department of Nuclear Medicine, relative to collaborative research in cancer detection.

U.S.S.R.

Joint American-Soviet cancer research activities during this fiscal year must be described as modest by comparison to previous years. In Moscow, U.S.S.R., from October 25 to 29, 1980, seven American scientists participated in a joint workshop on "Clinical Biochemical Pharmacology." The American visitors were provided with the opportunity to establish contact with excellent Soviet scientists with whom previous interactions had been relatively few. Some of the Soviet contributions were the result of their recent efforts with: (1) the selectivity of drug action and the administration of selectively localized drug-carrier complexes; (2) the selective activation of protective drugs and of protective metabolites; and (3) the biochemical and pharmacologic target-cell determinants of drug action for utilization in the design of "individualized therapy regimens."

One Soviet virologist spent 1 month in NCI and the Sidney Farber Cancer Institute exchanging information on general problems associated with viral carcinogenesis and/or cocarcinogenesis.

A second virologist spent 6 months in the Sidney Farber Cancer Institute (SFCI) engaging in three research projects. The first of these related to a comparison of the genomes of two murine leukemia viruses. One of these viruses, the Akv virus, replicates well in animals, but does not induce disease. The second, the SL3-3 virus, also replicates in mice, but induces a rapid T cell leukemia. Electron microscopic analysis of the comparative structures of the two viruses indicate that they are closely related. The second topic dealt with the structure of the section of the human chromosome that contains sequences homologous to the transforming portion of the genome of the feline sarcoma virus. The third study was one begun by the Soviet visitor in his U.S.S.R. laboratory that deals with the structure of the viruses derived from the Soviet baboon colony in Sukhumi, Georgia. Jointly, the scientists applied methods developed in SFCI for detailed analysis of RNA virus genomes to the Soviet materials and were successful in defining the viruses. The second and third studies are continuing, in parallel, in the U.S.A. and the U.S.S.R.

A Soviet geneticist spent 2 months at the State University of New York at Stony Brook for the purpose of mastering the technique of removing nuclei from cells and inserting these into the anucleated cytoplasm of cells of different origin. This enabled him and his American hosts to make "minicells" containing a few or a single chromosome and inserting these into cells of a different species. As a result, the Soviet scientist and his hosts were able to isolate and characterize a protein associated with cells that are resistant to genetically damaging agents such as colchicine. The concentration of the protein is directly proportional to variations in the length of the chromosome, which is amplified in the presence of an agent such as colchicine or methotrexate.

During the "Sixth American-Soviet Review of Problem 03.03—Malignant Neoplasia," September 13-22, 1981, proposals were discussed and, ultimately, agreement was reached to combine some of the existing programs under newly designated American-Soviet cancer priority areas and to discontinue, or limit, others. Thus, "Cancer Chemotherapy and Combined Modalities (Problem Area 03.0301)" is now designated as "Cancer Treatment." It will encompass activities related to Phase I and Phase II clinical trials; the exchange of preclinical and clinical drugs; collaborative studies on lung, breast, and ovarian cancers; and biologic response modification. Agreement was achieved by both sides to include the efforts currently under "Cancer Virology (Problem Area 03.0303)" and "Mammalian Somatic Cell Genetics Related to Neoplasia (Problem Area 03.0304)" as major components of the newly titled area of "Carcinogenesis." Select studies of chemical and physical carcinogens would be included as well. "Cancer Prevention" is the third new designation, and would include some of the current joint studies in cancer epidemiology, pathomorphology, and end results of cancer treatment. Chemoprevention is likely to have special significance as a focus for future cooperative endeavors in large-scale clinical trials of agents currently considered to possess preventive activity.

Activities with International Agencies: The International Cancer Research Data Bank (ICRDB) Program

The ICRDB program, established by the National Cancer Act of 1971, has developed into an effective, multifaceted system for the rapid exchange of cancer research findings among scientists. This international resource for cancer information is comprehensive and of service to cancer researchers throughout the world. To facilitate the transfer of available cancer research information, the ICRDB program has: established three on-line computer data bases which enable scientists to retrieve cancer information at more than 2,000 locations within the United States and in 13 countries; developed a series of publications providing complete coverage of cancer research information, in special formats designed for easy use and quick reference; and supported a variety of specialized information collection, analysis, and dissemination activities.

The Computer Data Bases of the CANCERLINE System

CANCERLIT, CANCERPROJ, and CLINPROT are the three data bases that make up the CANCERLINE System.

CANCERLIT contains more than 275,000 substantive abstracts of information accumulated from published papers and those presented at scientific meetings, symposia, and conferences; books; technical reports; and research theses. CANCERLIT is growing at an annual rate of nearly 50,000 abstracts, selected from over 3,000 biomedical journals. Through monthly updating of CANCERLIT, the most recently published research results are quickly available to cancer researchers worldwide. Since early 1980, all new literature entries have been indexed with the medical subject heading (MeSH) vocabulary developed by the National Library of Medicine (NLM), making their retrieval easier during on-line searching. ICRDB program screening, indexing, and abstracting activities are performed under contract by the Franklin Research Center in Philadelphia.

Descriptions of some 20,000 current cancer research projects in 83 countries are the elements of the CANCERPROJ data base, the most comprehensive source available for ongoing cancer research project information. Included are nearly 6,000 foreign project descriptions collected by an international network of data input coordinators. Collection, input, and quarterly updating of the project descriptions in CANCERPROJ are performed by the Current Cancer Research Project Analysis Center (CCRESPAC) under an inter-agency agreement with the Department of Commerce.

Summaries of nearly 2,800 experimental cancer therapy protocols are the substance of CLINPROT, the data base providing worldwide access to information on new procedures, agents, and combinations of modalities/agents being evaluated for treating cancer patients in major American and foreign cancer centers. Collection and input of protocol summaries and quarterly updating of CLINPROT are the contractual function of Informatics, Inc.

The cancer information contained in the data bases of CANCERLINE is available through the computerized biomedical information network of the National Library of Medicine. Foreign access to the ICRDB has been enhanced by the recent addition of CANCERLINE to the EURONET system operated by a consortium of the major hosts in the European Community offering on-line scientific and technical information and interactive retrieval services. NLM's effort in CANCERLINE is supported by an intra-agency agreement.

ICRDB Program Publications

CANCERGRAMS are published monthly as current awareness bulletins containing abstracts of recently published literature in 66 major cancer research areas. Each month, CANCERGRAMS are compiled from carefully selected and organized abstracts screened from over 3,000 biomedical journals. They are prepared for publication by scientists at three Cancer Information Dissemination and Analysis Centers (CIDAC's). CANCERGRAMS enable scientists to keep up with the

most relevant portions of the vast cancer literature with minimum time and effort.

SPECIAL LISTINGS of current cancer research are annual compilations of ongoing research projects in 55 different cancer problem areas. They are extracts from the CANCERPROJ data base, prepared by scientists at a Current Cancer Research Project Analysis Center. They are intended to stimulate interaction between investigators pursuing related avenues of research.

Ten to 20 ONCOLOGY OVERVIEWS are published each year. Each of the OVERVIEWS contains retrospective bibliographies, with abstracts, of recent literature and provides comprehensive coverage of specific topics of high current interest to cancer researchers. Included are the most relevant abstracts published during the past several years on the OVERVIEW topic, providing indepth coverage of emerging foci of cancer research. OVERVIEWS are prepared by scientists at the CIDAC's, with review and editorial commentary by well-known researchers in each topic area. They provide a rapid means of updating knowledge in burgeoning areas of cancer research.

The Compilation of Experimental Cancer Therapy Protocol Summaries

Now in the 5th edition, 1981, the compilation is derived from the CLINPROT data base and contains over 1,500 summaries of Phase II and Phase III clinical trials currently in progress in cancer centers of the world. The compilation is indexed by tumor, agent, and protocol identification number, and provides a useful reference for the practicing oncologist. Protocols which have been closed to patient entry during 1980 are listed by name of the principal investigator and include a mailing address. The 5th edition also includes a history of the Phase I protocols which were activated in 1980.

The *Directory of Cancer Research Information Resources*, 3rd edition, 1981, contains over 900 entries covering the broad spectrum of resources available to health professionals.

Special Information Activities of the ICRDB Program

Three contract-supported cancer information dissemination and analysis centers (CIDAC's) function as information resources in three broad areas of cancer research. These are the CIDAC for Diagnosis and Therapy, University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston; and the CIDAC's for Carcinogenesis and for Cancer Virology, Immunology and Biology, both at the Franklin Research Center, Philadelphia. Each CIDAC is staffed by scientists and served by a consultant network with special expertise in the appropriate fields. Within their own subject areas, CIDAC's prepare CANCERGRAMS and ONCOLOGY OVERVIEWS, perform custom CANCERLINE searches, and provide scientific guidance to the ICRDB program.

The current cancer research project analysis center (CCRESPAC) collects and processes ongoing research project information, generates the CANCERPROJ data base, and prepares the SPECIAL LISTINGS OF CURRENT CANCER RESEARCH. Custom data base searches are performed on request.

The Clearinghouse for Ongoing Research in Cancer Epidemiology is a cooperative project supported jointly by the ICRDB program, the International Agency for Research on Cancer (IARC) in Lyon, France, and the German Cancer Research Center in Heidelberg, Germany. The CLEARINGHOUSE, located in Lyon, collects, processes, and disseminates detailed data on research related to cancer epidemiology and studies of human cancer causation in countries throughout the world. The CLEARINGHOUSE also prepares lists of epidemiology researchers and resources, responds to technical questions, and produces an annual *Directory of Ongoing Research in Cancer Epidemiology*. The 1981 edition of the directory contains 1,313 abstracts of epidemiology projects in 80 countries.

The Latin American Cancer Research Information Project (LACRIP) was developed through the ICRDB program in collaboration with the Pan American Health Organization (PAHO) and its Regional Library of Medicine (BIREME) in São Paulo, Brazil. LACRIP serves as the source for identifying, collecting, and supplying Latin American biomedical literature, summaries of ongoing cancer-related research projects, and active therapy protocols for inclusion in the CANCERLINE system. PAHO also serves as the center for searching ICRDB data bases and providing documents and data in response to requests for information from cancer researchers in Latin America. An automatic SDI service is also provided to cancer researchers and clinicians in Latin America.

Through LACRIP, a series of collaborative clinical studies has been developed between nine cancer centers in the United States and six centers in Latin America. LACRIP maintains the clinical data gathered at the Latin American centers and arranges for the exchange of professional staff between centers in order to promote a better understanding of the current cancer treatments available in the United States.

In cooperation with the the International Union Against Cancer (UICC), the ICRDB program provides partial support for a special Committee for International Collaborative Activities (CICA) within the framework of the UICC. One of the CICA activities is the collection of data on ongoing cancer research projects (including clinical protocols) from 72 countries. CICA personnel identify and promote collaborative projects among cancer centers and cancer scientists in different countries. CICA periodically publishes an updated *International Directory of Specialized Cancer Research and Treatment Establishments*, which contains descriptions of more than 700 of the world's cancer centers. An International Cancer Patient Data Exchange System (ICPDES) has been established as part of the CICA project. Present participants include nine European and five American cancer centers. The ICPDES is the first internationally recognized and standardized tumor registry, providing comparative data of value in cancer treatment and prevention from a multitude of countries.

Scientist-to-Scientist Communication

The ICRDB program, through the UICC in Geneva,

Switzerland, encourages international scientist-to-scientist communication through the International Cancer Research Technology Transfer program (ICRETT). This program promotes direct and rapid transfer of information about new or improved technology or methodology between investigators located in different countries. This is accomplished by supporting short-term visits for the purpose of conducting brief collaborative research projects by investigators working in different countries. Since the inception of the program in 1975, 534 ICRETT awards have been granted (through September 1981).

In many instances, ICRETT associations between scientists from different countries develop into significant collaborative studies that otherwise might not have had the impetus and resources with which to evolve. For instance, an area of study known as "chrononcology" is attracting the attention and interest of many oncologists. The phenomenon relates to optimum timing of drug administration during the daily cycle, the 24-hour temperature pattern of tumors, etc. In this context, a chrono-oncologist and ICRETT awardee from the University of Minnesota journeyed to Chandigarh, India, to demonstrate radiation therapy and surgery-radiation therapy procedures and methodologies in the clinical management of cancer. He introduced the Indian oncologists to chronobiology (24-hour biology cycle) and chronochemotherapy and their relationship to immunobiology and immunotherapy. In the course of his visit, he arranged for his group to be consultants and to assist the Indian scientists in the analysis of data emanating from their studies.

Subsequently, an oncologist from Karnataka, India, utilized the resources of his ICRETT award to study in the Chronobiology Laboratories of the University of Minnesota. He and his hosts collaborated on analyzing clinical data obtained in India for the tumor temperature patterns of carcinoma of the cervix. They then studied the effects of adrenocorticotrophic hormone—ACTH—as pretreatment for improving patients' tolerance of Adriamycin when administered at certain hours of the day.

A Liberian epidemiologist/biometrist observed and learned the principles for organizing a cancer registry during her period of ICRETT study in Dundee, Scotland. Her objective was to develop skills for improving methods in Liberia for the registration of new cancer cases and for followup studies of cancer morbidity/mortality.

While in the National Cancer Institute, an ICRETT-sponsored Yugoslav immunologist studied techniques for the isolation, purification, and characterization of lung tumor-associated antigen. There now is a continuous exchange of information on the results of the use of this antigen—a glycoprotein containing sialic acid—in the immunodiagnosis of human lung tumors.

With the assistance of his ICRETT award, an epidemiologist from the People's Republic of China visited cancer registry facilities in Birmingham and Oxford, England, and Lyon, France, where he benefited from their design and experience with systems for registration of cancer incidence and followup. Of

importance to him was familiarization with methodologies used to catalog and correlate information for use in studies of cancer risk factors and etiology. His training and application of it will be of significance in effective collaboration on problems of cancer epidemiology in progress under the American-Chinese Cooperative Cancer Program.

The NIH Visiting Program

During 1981, personnel of the National Cancer Institute served as hosts for scientists from 38 countries who came to the United States to engage in collaborative cancer research activities. There was a total of 244 foreign visiting scientists, associates, and fellows. Nine of the visitors were appointed as Experts, and 42 came as Guest Researchers whose financial support comes from sources other than NCI. The activities of these scientists were pursued in the laboratories of the NCI Divisions of Cancer Treatment, Cancer Cause and Prevention, and Cancer Biology and Diagnosis.

These associations are mutually beneficial. NCI host scientists are afforded opportunities to learn about cancer problems in a given foreign country; about factors peculiar to that nation that might be related to morbidity and mortality of cancer; and about activities under way concerning the management, treatment, and prevention of cancer. On the other hand, the foreign scientists are provided with unique opportunities to improve their mastery of the scientific method or to develop their potential for significant contributions to basic and/or clinical research. The value of such scientific interaction can be assessed ultimately on the knowledge that cancer patients throughout the world are benefiting from an improved quality of care.

Extramural Programs

During 1981, the Divisions of Cancer Biology and Diagnosis, Cancer Treatment, and Cancer Cause and Prevention maintained extensions of their programmatic objectives in foreign countries through 34 contract research activities, compared to 53 during the previous year. The Division of Extramural Activities provided fiscal support, through 52 grants, to scientists in foreign institutions conducting basic and applied cancer research.

The Division of Cancer Treatment (DCT)

DCT research contracts have been awarded to investigators in 11 institutions of six foreign countries for studies related to the characterization of anticancer agents; the search for potentially useful anticancer agents; the screening and testing of such compounds; and clinical trials on specific cancers. Examples of this international collaborative effort follow.

In 1972, DCT established a "Cancer Chemotherapy Research Collaborative Office" at the Institut Jules Bordet in Brussels, Belgium. This facility provides an important service function to cancer researchers and clinicians in the U.S.A. and Europe as a center of reference for the vast amount of pertinent information on ongoing cancer research programs in both continents. Its "liaison function" has been invaluable in promoting cooperative studies in experimental and

clinical pharmacology and in clinical trials. In this context, there is a direct association with the European Organization for Research on the Treatment of Cancer (EORTC), which, among other activities, collects and manages data on clinical trials for Europe and serves as the coordinating center for clinical cooperative groups. By this means, the EORTC facilitates data collection, at a much faster rate, on the clinical evaluation of new drugs and therapeutic results from a large number of patients. Currently, there are approximately 64 clinical studies in progress among the EORTC clinical cooperative groups. Two hundred and fifty-five institutions in 13 countries are involved in the trials and, currently, 6,500 European patients are monitored by the EORTC data center. Since 1972, more than 25,000 new compounds have been collected through the direct efforts of the Collaborative Office, and several of these proved to be interesting enough for development toward clinical trial.

DCT's maintenance in Tokyo, Japan, of a "Collaborative Office for Cancer Chemotherapy Research" contributes significantly to NCI's cancer treatment program. On the order of 35 to 40 potentially useful drug materials are collected per month, including synthetic preparations and products of natural origin. During the period spanning June 1979 and June 1980, 390 synthetics and 67 natural products were collected from 34 Japanese institutions. Active new materials include synthetic cyanines; analogs of 5-fluorouracil, cytosine arabinoside, and imidazolyl carboxamide; and nitrosoureas. Among the natural products are fatty acid esters of a crude nagilactone mixture, and anthracycline antibiotics.

There is a continuation of cooperative preclinical and clinical research associations between American cancer centers and those of the *United Kingdom*, stimulated largely through DCT efforts and its partial support. The Institute of Cancer Research in London is contributing significantly to the DCT mission through research encompassing: drug development and screening; preclinical toxicology; clinical Phase I-II testing; drug rescue strategies and scheduling; and collaborative pharmacologic and clinical testing of new drugs.

In *Italy*, DCT supports in part the coordinating center for clinical study of melanoma in the National Institute of Oncology in Milan. There, controlled clinical trials are continuing on breast cancer, gastrointestinal cancer, and tumors of the brain. The Mario Negri Institute in Milan screens potential anticancer compounds that are available in Europe, emphasizing studies of their pharmacology.

In association with the University of Dar Es Salaam in *Tanzania*, DCT is engaged in a study of the use of oral 13-cis retinoic acid as a chemopreventive agent of skin cancer in albino Africans. These people, living in the equatorial zone, are subject to the most intense ultraviolet irradiation on the surface of the earth and are candidates, virtually, for a 100 percent increase of skin cancer.

Three years ago, DCT entered into a cooperative relationship with *Latin American* cancer institutes by

virtue of the NCI-PAHO Collaborative Cancer Treatment Research Program (CCTRP). Clinical research activities are being pursued jointly by investigators in 10 Latin American cancer institutes and hospitals and 8 American cancer centers. Currently, there are 28 active treatment protocols being evaluated. These include therapeutic concepts in hematologic malignancies, childhood malignancies, osteosarcomas, and testicular cancer. Multimodal concepts in solid tumors are being pursued in advanced breast and head and neck cancer. Systemic therapy of solid tumors is being evaluated in advanced breast cancer, advanced gastric cancer and adenocarcinoma, and sarcomas. Since the inception of this multinational effort, 1,158 patients have been entered in the program.

The Division of Cancer Cause and Prevention (DCCP)

DCCP is very active in its associations with international organizations and agencies which have well-defined objectives in cancer research, especially its cause and prevention. DCCP is engaged in collaborative contract research in eight institutions and agencies in six foreign nations. These foreign extensions of the DCCP program enable the Division to support fundamental studies on normal and malignant cells in relation to such carcinogens as viruses and chemicals, as well as epidemiologic studies of human populations for the identification of risk factors predisposing to various cancers. These studies are primarily conducted under three major programs: Biologic Carcinogenesis; Chemical/Physical Carcinogenesis; and Epidemiology. Excellent model systems are available to scientists studying the effects of potentially carcinogenic factors in the environment.

Contributions to the scientific advance in the Biologic Carcinogenesis program, for example, include the discovery of a DNA virus—Epstein-Barr virus (EBV)—provided impetus to a period of research to establish a causal relation to Burkitt's lymphoma (BL) and to nasopharyngeal carcinoma (NPC). Studies were focused on populations of African and Asian patients, respectively, as sources for test materials. The emphasis was on the detection and incidence of BL cases in West Africa and the possible role of malarial infection as a contributing factor. NPC cases in the Hong Kong and Singapore regions of East Asia have been entered into the computer system of the International Agency for Research on Cancer (IARC) for analysis and determination of whether certain genotypes place individuals at high risk to this cancer. Serologic tests for the detection of antibodies to various viral or viral-associated antigens in patients and controls continue to show a strong association of EBV with lymphoproliferative disease and help define populations that are susceptible to its progression.

Several investigations, under the Chemical Carcinogenesis program, are designed to determine the mechanism of action of chemical and physical agents in the transformation and progression of a cell from the "normal" to the malignant state. These foreign studies are targeted toward the understanding of the interaction of activated metabolites of carcinogens with nucleic acids, both RNA and DNA, of the cell. Thus, they are

attempting to define the mechanism of alkylation of N-nitrosamines and their derivatives and determine the DNA adducts generalized by exposure to benzo(a)pyrene and other hydrocarbon carcinogens. Other studies have long-range objectives for developing models to analyze and understand the steps in the carcinogenesis process by defining cellular preneoplastic changes in epithelial cells following exposure to liver carcinogens and developing short-term assays for the detection of chemical carcinogens.

The Epidemiology program includes studies on the natural history of cancer in humans and on the incidence of cancers in different geographic locations so as to identify intrinsic and extrinsic risk factors. Many surveys are conducted in countries throughout the world, thus permitting comparison with the incidence of various cancers in the United States. Excess thyroid nodular disease, for instance, was detected following low-level exposure of children receiving X-ray therapy for ringworm of the scalp. Studies on the risk of developing second cancers among former cervical cancer patients given low-level doses of radiation suggest excess risks to other cancers such as bladder, rectal, kidney, and ovarian.

Two new studies in the Epidemiology program hold the promise for highly significant information. One is a pilot study initiated to determine the basis of cancers of the esophagus and nasopharynx occurring in the populations within the People's Republic of China. The second relates to cancer incidence in various ethnic groups residing in Israel and for similar groups residing in the United States. It will permit the comparison of trends in cancer incidence among persons in two different geographic locations, and among second-generation immigrants.

Among the notable activities in the Environmental Carcinogenesis program are the IARC Monographs on the "Evaluation of the Carcinogenic Risk of Chemicals to Humans." The 1980 compendium entitled, "Chemicals and Industrial Processes Associated with Cancer in Humans," serves as a source, for example, of the list of chemicals being tested for carcinogenicity in laboratories throughout the world. They reflect the international consensus on these agents and have become indispensable reference sources to scientific pursuits on carcinogenesis.

The Division of Extramural Activities (DEA)

Grants by the DEA have been made available to 37 institutions and organizations in 13 countries. The scientific investigations include both basic and applied research. Among these are assays for and studies of the action of carcinogens and "promoters" of carcinogenesis by personnel of the National Research Council of Canada. At the University of London, a study is under way on the therapeutic response of human tumor xenografts. At the University of Helsinki in Finland, studies are being pursued to determine glycoprotein differences in normal and malignant human blood cells. Scientists of the Weizmann Institute in Israel are engaged in research on the immunobiology of tumor metastasis.

NATIONAL EYE INSTITUTE

Introduction

Today, as many as 40 million people in the world are blind, and in 20 years, this number may double. Eighty percent of blindness is preventable or curable, and a major new international effort to eliminate blindness is under way. The National Eye Institute (NEI) is participating in the U.S. activities aimed at the prevention of blindness by evaluating and helping to establish the research base for development of effective prevention and treatment programs. Specifically, the NEI program is aimed at:

- Obtaining sound epidemiologic data on the prevalence of visual impairment and blindness.
- Evaluating available health technologies, promoting programs that are the most cost-effective, and making these available to affected populations.
- From this research, stimulating the controlled, clinical evaluation of findings which appear to be effective.

Bilateral Agreements and Other Country-to-Country Activities

India

Meetings between U.S. and Indian scientists were held in Hyderabad, India, in October 1980 and in Bethesda, Maryland, in May 1981 to establish research protocols to be carried out at the center and develop the administrative structure of the Collaborative Clinical Research Centre for the Prevention of Blindness.

Deficient nutrition is the leading cause of blindness in children worldwide. In India alone, 20,000 children become blind each year from nutritional deficiencies; 10,000 of these children survive, and 10,000 die within 1 year. However, the research base exists, primarily from work done in the U.S., to mount an applied clinical research program to identify those children who present the highest risk of going blind, determine ways to prevent this condition, and develop more cost-effective programs so as to target vitamin A to the highest risk populations. Such a program has been established, culminating in a series of workshops held over the past year in India and the U.S. This has resulted in the establishment of a Collaborative Clinical Research Center for the Prevention of Blindness at Hyderabad, India. The following is a list of projects to be carried out jointly in the center:

- Relationship between measles, keratomalacia, and

blindness in children.

- Effect of ascariasis and deworming on vitamin A nutritional status of children.
- Anterior segment collagenase activity and keratomalacia.
- Absorption of vitamin A in diarrhea, treated with or without oral rehydration solution.
- Immunity and infection in relation to vitamin A status.
- Evaluation of the relative dose response (RDR) for identifying subclinical vitamin A deficiency in children.
- Case control study of xerophthalmia in children.

Final approval of the research agreement formalizing this arrangement has been received from the Government of India and is pending on the U.S. side. It is expected that the Center will commence operations in early 1982.

Japan

The U.S.-Japan Memorandum of Understanding (MOU) on Vision Research has been ongoing since April of 1976. The MOU provides for an exchange of scientists between the National Eye Institute and the Japan Society for the Promotion of Science. Two scientists per year from each country may be selected for the exchange—one short-term (2 weeks to 3 months) and one long-term (3 months to 1 year).

The stated objectives of the MOU are to foster better communications and interactions between vision research scientists in Japan and the U.S.; to broaden the base of vision research through cooperative efforts; and to bring about better utilization of existing resources for vision research in both countries. Through the exchange of scientists, the objectives were accomplished in 1981.

In October 1981, a scientist from the University of Tokyo, joined a scientist from the NEI in the investigation of transport system in the anterior uvea for nonsteroid *weak* acid anti-inflammatory agents. The Japanese scientist proposed to study the time course of the accumulation of radioactive aspirin or other nonsteroid anti-inflammatory agents in the isolated ciliary body, the saturation kinetics of the accumulations, and the effects of certain agents. He will study how the above transport system is related to the intra-ocular pharmacokinetics of such agents in *in vivo* condition.

Another scientist from the University of Tokyo spent November visiting major eye research centers and exchanging information on the fine structure of

photoreceptive membrane and on the plasmalemmal specialization of retinal cells in cuttlefish.

There were two short-term American visitors to Japan in 1981. The first, from Case Western University, spent a month each at the Kobe University Medical School and the University of Kyoto and attended the 6th International Symposium on Glycoconjugates. He pursued structural studies on the oligosaccharides of glycoproteins and glycolipids and worked with the culture of cells from the neural retina and retinal pigmented epithelium. The second, from the University of California, visited the Kanazawa University to conduct studies of plasticity of single cortical neurons during physiologic study. Earlier studies in amblyopia and strabismus using animal models were continued and analyzed.

The Memorandum of Understanding will be negotiated for a 3-year renewal in April 1982, as both parties feel this program to be a valuable exchange.

U.S.S.R.

A meeting to review progress on the Vision Research Section of the U.S.-U.S.S.R. Program for Health Cooperation was held in October 1981 between the Director, NEI, and the Director, All-Union Research Institute of Eye Diseases. Considering the magnitude of public health problems caused by eye disease and the knowledge and research accomplishments of investigators in the United States and the Union of Soviet Socialist Republics, the need for continued collaboration on vision research aimed at the prevention of eye diseases and blindness and the alleviation of suffering caused by these diseases was reaffirmed. Progress in each problem area was documented in 1981. These areas are:

- Use of Q-switched laser in the treatment of glaucoma.
- Assessment of critical flicker fusion (CFF) to determine optic nerve function.
- Assessment of gratings to determine optic nerve function.
- Clinical trial of ENKAD treatment of retinitis pigmentosa.

Activities with International Agencies

World Health Organization (WHO) — A Programme for the Prevention of Blindness

The Director, NEI, continued to serve as a member of the World Health Organization's Special Advisory Panel on the Programme for the Prevention of Blindness. This group has been established to advise WHO in its efforts to eliminate blindness worldwide. The advisory group held its annual meeting in New Delhi, India. The major areas discussed were:

- The economic implications of blindness prevention.
- Activities of collaborating centers for the prevention of blindness.
- Research priorities in the Programme for the Prevention of Blindness.

The Programme for the Prevention of Blindness, which is primarily supported by the National Eye Institute, has expanded its collection of data on blindness and its causes over the past year. Several

additional blindness surveys are being developed in Asia and Latin America in addition to the survey plans in Mali and Togo that were developed in 1981 and will be carried out in 1982.

Activities of NEI as a WHO Collaborating Center

The NEI continued to serve as a WHO Collaborating Center for the Prevention of Blindness. The functions of this center were:

- To provide facilities for the training of personnel in epidemiology and biostatistical techniques.
- To conduct applied field research on the epidemiology, management, and operational aspects of avoidable blindness.
- To foster a multidisciplinary approach to the promotion of eye health and to delivery of eye health care to all.
- To participate in the collection, evaluation, and distribution of pertinent information.
- To provide advisory services and expertise on request.
- To conduct research into low-cost, innovative approaches to conduct surveys of blind and visually impaired persons.

Specific activities carried out in 1981 were:

Workshop on Operations Research and Mobile Camp for Cataract Surgery

In October 1980, a workshop was held on operations research and mobile camps for cataract surgery. The Director, NEI, was a major organizer and contributor to this meeting. The workshop examined the feasibility of applying techniques of operations research in India, where 1.5 million people go blind every year, and where 6 million people are blind from cataracts. Various mathematical models for solving this problem were discussed as well as organizational approaches. An operations research approach was viewed as most promising by the participants, and demonstration projects to test various models will be developed.

Evaluation of a Research Program in Eye Health for the Government of India

The National Eye Institute provided a short-term consultant to the Government of India to:

- Review the recommendations of the National Group on Research in Eye Health and ICMR Advisory Panel and Ophthalmic Sciences.
- Formulate project protocols for research on problems identified for priority attention.
- Recommend collaboration with national and international workers and institutions.
- Identify and select resources for implementing the research activities.

Strategic Approaches to Prevent Blindness

The NEI is providing planning expertise to the WHO in the development of strategic approaches to prevent blindness. This is the first stage in the development of a planning framework in which an accelerated and expanded international prevention of blindness program should operate. The areas of emphasis are cataract, trachoma, onchocerciasis, nutritional blindness, ocular trauma, and glaucoma.

European Office of WHO Meeting on the Use of Residual Vision by Visually Impaired Disabled Persons

The NEI participated in a multidisciplinary meeting, consisting of representatives of national research organizations, professors of visual science, ophthalmologists, representatives of private societies for the visually disabled, and WHO staff members, to review the status of services and research in the field of visual impairment. The categorization of visually impaired disabled and handicapped persons still presents conceptual and organizational difficulties. The meeting therefore discussed criteria for the categorization of persons with residual vision, assessment of their number, and the different problems they face. Special attention was paid to the availability and assessment of existing technology and to the need to develop appropriate and simple technology which would enable people with residual vision to maintain their independence. The nature of existing services and the available manpower were also reviewed with the aim of filling gaps as perceived by both professionals and consumers, and to formulate recommendations for action in the context of the International Year for Disabled Persons and interdisciplinary research in priority areas.

WHO Consultant

The NEI hosted a scientist from the Department of Biochemistry, Institute of Post Graduate Medical Education and Research, Calcutta, India. As a consultant at the NEI, he engaged in cooperative research activities aimed at the application of advanced biochemical techniques to the development of new diagnoses and treatment approaches for children suffering from nutritional deficiencies. Specifically, he was able to work with U.S. experts on techniques of tubulin biosynthesis and microtubule assembly in normal and vitamin A-deficient animals exhibiting kerophthalmia.

Clinical Trial of Steel Sutures

NEI staff have been assisting in the development of a randomized clinical trial involving approximately 4,000 patients assigned to either conventional or vanadium stainless steel sutures in cataract surgery. The study is planned to be conducted in India, and will evaluate the safety and efficacy of this suture material, and its potential for reducing the postoperative stay. There is a large backlog of cataract cases awaiting surgery in India. If steel sutures prove effective and also permit shortening of the postoperative recovery period, then this backlog can be reduced.

Development of a Cataract Instrument

NEI intramural scientists, Indian scientists from the Aravind Eye Hospital in Madurai, and engineers from the National Aeronautics and Space Administration have been working for several years to develop a more effective instrument for removing cataracts. This involves developing and evaluating a technique for removal of hard cataracts through a small incision with an air turbine device. During the past year, the technique and the instrument have been refined and

successfully tested in animals and on hard cataracts from Indian patients *in vitro*. Trials have been initiated on a series of blind eyes with hard lens in India by Indian ophthalmologists on the research team. This instrument and surgical technique have great potential for shortening the postoperative recuperative period for cataract patients, which has been one of the principal logistical problems in making cataract camps and mobile units more effective. The next steps are the simplification and miniaturization of the tool.

WHO Immunology Course

NEI scientists participated in the Immunology Course which took place at WHO Headquarters in Geneva and in Epalinges. This course presents a unique opportunity to contact the finest Third World immunologists. Before this NEI participation, there was no aspect of ocular immunology touched upon in the course. The course provided an opportunity to present various aspects of ocular autoimmunity, ocular immunoregulation, and ocular parasitic diseases. It is hoped that the course will kindle enough interest in further research, since major problems in the Third World—onchocerciasis, leprosy, and toxoplasmosis—all have ocular manifestations.

Health Scientist Exchange Programs and NIH Visiting Program

Visiting Scientists in the NEI Intramural Program have contributed to a number of major advances made in vision research. The enzyme aldose reductase appears to be involved in the initiation of a number of diabetic complications. Visiting Scientists were actively involved in experiments in which aldose reductase inhibitors were used in preventing cataracts and ameliorating the adverse diabetic effects on the cataracts.

Another major area in which Visiting Scientists are involved is in the research in ocular immunology. Uveitis is a major ocular problem in that rational means of treatment have not been developed. NEI scientists have made significant advances in developing a mode of treatment for certain types of uveitis.

The Visiting Scientists program has been invaluable to the Intramural Program because it serves as a means of attracting top scientists and ophthalmologists who have special expertise. They have enhanced the intellectual environment of the Institute.

Other Extramural and Intramural Support

The extramural and intramural components are supporting epidemiologic and biomedical research in the areas of cataract, corneal infections, and the development of new drug therapies that have great potential for preventing or treating these diseases. Especially important here are the investigations into the relationship of vitamin A to nutritional blindness, which could result in the near future in clinical applications that will help prevent this leading cause of childhood blindness worldwide.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Introduction

The National Heart, Lung, and Blood Institute's (NHLBI) programs in heart, blood vessel, lung, and blood diseases and blood resources are receiving worldwide attention. These disease problems are of major significance and are shared to a greater or lesser extent by both industrialized and developing nations. Recent international statistics show dramatic shifts in the patterns of these diseases throughout the world. For instance, table below shows selected statistics comparing the United States with other countries in trends of cardiovascular disease, the number one cause of death in the United States and many other countries. The U.S.A. currently leads the world in the rate of decline of coronary heart disease. This is a marked change in view of earlier epidemic increases in cardiovascular deaths over many decades.

In recent years, there have been major changes in the initiation and development of the Institute's international activities. As a result, international programs and activities have expanded significantly. Three factors have played important roles in this development. First, the National Heart, Lung, and Blood Program mandated by the President and the Congress in 1972 has significantly broadened the scope and depth of the Institute's national programs, thereby providing new opportunities for meaningful international collaborative efforts. Second, the Department of Health and Human Services and the Department of State have encouraged the strengthening of international cooperation in medicine and health. Third, the scientific and medical leadership of many other countries has shown an increased interest in the Institute's programs and activities and in efforts to enhance international collaboration, particularly in the cardiovascular area, but also increasingly in the lung and blood diseases areas. Increased international attention to the Institute's programs has been catalyzed by the recent success in the United States in bringing about a significant decline in cardiovascular disease.

Broad Goals

The NHLBI, in addition to supporting a vigorous national program of research, prevention, and control of heart, lung, and blood diseases, also maintains an active and open exchange of scientists and information with many countries whose health problems are similar

International Trends in Mortality Rates for Coronary Heart Disease Age-adjusted, Males Age 35-74 Years: Selected Countries 1977 and 1969

Country	Rate per 100,000 Population		Difference in	
	1977	1969	Death Rate	
U.S.A.	650.4	864.7	Decrease	214.3
Australia	649.0	843.7		194.7
Israel	522.8	653.3		130.5
Canada	624.1***	703.3		79.2
Norway	540.6	583.0		42.4
Japan	99.2	123.3		27.1
New Zealand	747.1***	773.4		26.3
Belgium	426.8***	446.1		19.3
Finland	878.0**	893.7		15.7
Italy	309.6*	313.0		3.4
Czechoslovakia	590.3*	587.9	Increase	2.5
France	207.0**	195.2		11.8
Netherlands	493.4	478.7		14.7
Denmark	584.6	566.1		18.5
England/Wales	685.6	662.1		23.5
Switzerland	320.8	290.4		30.4
Austria	460.1	428.3		31.8
Germany (FR)	466.1	427.3		39.3
Yugoslavia	227.6***	185.0		45.6
Sweden	587.6	524.0		63.6
Romania	248.2	170.5		77.7
Hungary	532.5	441.6		90.9
Bulgaria	423.5***	299.4		124.1
Poland	319.8	186.5		133.3

* 1976

** 1975

*** 1977

Source: Center for Health Statistics (ICD 410-413 Unpublished)

or related to our own.

The broad goals of the National Heart, Lung, and Blood Institute's international programs and activities are:

●To develop international activities relevant to the goals and priorities of the U.S. national programs in heart,

lung, and blood diseases and blood resources. These goals are set forth in the Institute Director's annual report to the President and the Congress on the National Heart, Blood Vessel, Lung, and Blood Program.

●To develop international contacts, activities, and programs of mutual interest and benefit to the United States and to the cooperating country or countries in areas related to the Institute's national mission.

Thus, the scope of the Institute's international activities and programs closely follows the scope of the Institute's national programs and priorities.

The broad goals of the NHLBI international programs include the design and implementation of international population studies, clinical investigations, and laboratory experiments to enhance and complement data generated in domestic studies on important aspects of heart, lung, and blood diseases and blood resources. As a result of this broadened scientific perspective, it is possible for U.S. and foreign scientists to develop joint international data bases and to draw international comparisons not possible with national studies alone. These international comparisons are important in understanding disease and in developing new approaches to treatment, prevention, and control.

With some countries, joint studies are designed for implementation by U.S. and foreign scientists with complementary skills, approaches, or facilities for studying the same problem. This leads to more cost-effective utilization of NHLBI funds to support research in particular areas. The experience of the NHLBI international programs supports the conclusion that some studies can be performed less expensively in other countries than is possible in the United States. The Institute seeks to maximize the scientific benefit from available research dollars by taking advantage of such opportunities for international cooperation, when offered by other countries.

The NHLBI international programs also focus on the discovery and analysis of new methods, treatments, techniques, and equipment which could be applied effectively through the U.S. biomedical research community, to the ultimate benefit of U.S. health care consumers. This goal is facilitated by international exchanges of information and data which offer clues to productive directions for further research and development.

Specific Impacts

Several recent international developments are likely to affect the future direction of the Institute's international programs. First, cardiovascular disease is the major health problem in many countries in the world, and concerted international action is being taken to deal with it. The Institute plans to continue to cooperate in these efforts. Second, developing nations are concerned that appropriate technology be introduced to deal with cardiovascular and other health problems in their countries, and the Institute has indicated an interest in increasing collaboration with these countries, keeping this goal in mind. Third, the designation

in 1980 of the NHLBI as the WHO Regional Collaborative Center for Research and Training in Cardiovascular Diseases for the Americas is likely to open up new opportunities for multilateral cooperation with Latin American countries as well as for the rest of the world.

During the past few years, many cardiovascular studies in the United States and other countries have indicated marked changes in the risk of cardiovascular disease among persons who migrate from one country to another, and among those who experience rapid "Westernization" in their home country. These findings have tremendous implications for public health. Because these changing patterns have occurred within relatively short time periods, they are evidence of environmental and lifestyle influences. It therefore follows that if we can define these environmental circumstances more precisely, we would open new pathways to disease prevention. Thus, it is anticipated that further international cooperation on the epidemiology of cardiovascular disease will benefit populations both in the United States and abroad. There is reason to believe that the answers to these disease problems will come more rapidly through carefully targeted international cooperative research on populations that vary widely in lifestyle, nutrition, and susceptibility.

Bilateral Agreements and Other Country-to-Country Activities

Canada

A major Institute activity is the carrying out of multicenter controlled clinical trials aimed at validating treatment or prevention of cardiovascular and pulmonary diseases. The following clinical trials have a major participating center located in Canada: *The Beta Blocker Heart Attack Trial*, the *Coronary Artery Surgery Study*, the *Lipid Research Clinics*, the *Multiple Risk Factor Intervention Trial*, the *Clinical Study of Intermittent Positive Pressure Breathing*, the *Nocturnal Oxygen Trial*, and the *Prevention of Neonatal Respiratory Distress Syndrome with Antenatal Steroids Administration Trial*. The Institute has also funded Canadian research aimed at modifying the development of atherosclerosis in rabbits by blocking the activity of the amino acid lysine in circulating lipoproteins through the use of drugs or dietary manipulation.

France

Under the NIH-INSERM (Institut Nationale de la Santé et la Recherche Médicale) Agreement signed in 1970, a 3-year cooperative study on interstitial (fibrotic) lung diseases was initiated in 1980 by intramural NHLBI researchers and their colleagues in Paris. Because of the increased frequency of interstitial lung disease during the past two decades, this problem is receiving increased attention among scientists. The U.S.-France exchange program in this area was established to share scarce patient biopsy materials, thereby making it possible to undertake a variety of large-scale studies on the pathology of these diseases. The incidence and significance of Langerhans cells in lungs of more than 100 patients with various types of pulmonary fibrosis

have been studied, and the results have been published. A study on histiocytic disorders and another on hypersensitivity pneumonitis are completed, and the results have been submitted for publication. Other joint projects being pursued at the present time include: a general review and revision of the criteria for the diagnostic classification of interstitial lung disorders on the basis of histological and electron microscopic findings; studies of the ultrastructure of Langerhans cells in histiocytosis S; studies of pulmonary ultrastructure in sarcoidosis and other diseases in which granulomas develop in the lung; ultrastructural studies of the pulmonary vasculature in interstitial lung diseases; and studies of the morphology of abnormal collagens found in diseased lungs. All of these studies have been made possible by the pooling of materials and the collaboration of U.S. and French researchers.

Under the auspices of the NIH-CNRS (Centre Nationale de la Recherche Scientifique) Program for Scientific Collaboration, a young U.S. physical biochemist spent 8 months investigating an important area of lipoprotein structure and function at the CNRS Center for Molecular Biology in Orléans. She studied mechanisms by which serum lipids and apolipoproteins interact to form the stable native lipoproteins that circulate in the blood. The results of this research provided further insight into the atherogenetic process and the protective role of high-density lipoproteins against plaque formation.

The NHLBI has initiated a Primary Reference Materials Program for hemocompatible materials to be used in cardiovascular prostheses. French researchers working in the biomaterials area have requested that they receive such reference materials when these become available.

Federal Republic of Germany (FRG)

The U.S.-FRG cooperative activities in the cardiovascular area are conducted under the auspices of a Joint U.S.-FRG agreement between the DHHS and the Federal Ministry for Research and Technology of the Federal Republic of Germany on Cooperation in the Field of Biomedical Research and Technology. The original 5-year agreement in 1976 was extended for 5 years in 1981. The emphasis is on linking ongoing projects in the two countries in two areas: arteriosclerosis and hypertension.

The German side wishes to duplicate the U.S. decline of cardiovascular disease and has initiated a national program modeled on the U.S. National High Blood Pressure Education Program. A risk factor intervention study also is being planned. Pilot studies are under way to gather the necessary epidemiological background data and to clarify the methodological approaches most suitable for use in the FRG.

A Joint U.S.-FRG Workshop on Multiple Risk Factor Intervention Trials was held in Heidelberg in April 1981, where the following topics were addressed: Concepts of Intervention in Unselected Populations; Concepts of Evaluation for Cardiovascular Intervention; Elements of Hypertension Programs; and Recommendations for German-American Cooperation. At a

colloquium following the workshop, the U.S. delegates' experiences with community-based cardiovascular disease prevention programs were presented. A second workshop in Munich focused on epidemiology and preventive medicine and hypertension control in community-based prevention programs. During joint scientific and health policy discussions held in Heidelberg, Bonn, Munich, and Berlin, it was decided to consider cooperative activities in the following areas during the next two years:

- International comparable surveillance and monitoring of cardiovascular morbidity and mortality and their association with risk factors and health practices.
- Development and exchange of techniques and strategies for intervention studies.
- Development and exchange of techniques for evaluation and validation of approaches to intervention.

A U.S. scientist visited the FRG in 1981 for joint discussions of the planned Multi-Center Intervention Trial and the health information survey that is needed to provide background information for the main study. An FRG delegation visited the U.S.A. in October 1981 to discuss detailed methodology and resolve specific problems that may arise during the survey.

Greece

An Agreement between the Government of the United States of America and the Government of the Hellenic Republic for Cooperation in the Economic, Scientific and Technological, and Educational and Cultural Fields was signed in April 1980. Preliminary exchanges of information in the area of the hemoglobinopathies have taken place under this agreement. The NHLBI has had informal cooperative activities with Greek scientists for many years. These involve the epidemiology of atherosclerosis and the hemoglobinopathies, particularly thalassemia (Cooley's Anemia).

Hungary

Science and Technology Agreement between the Hungarian People's Republic and the Government of the United States of America on Cooperation in Culture, Education, Science, and Technology was renewed in December 1981. Article II of the Agreement calls for exchange and cooperation in fields of pure and applied science as well as technology on the basis of mutual benefit and common interest. The Hungarian Deputy Minister of Health visited the NHLBI in 1980 to continue exchange of information and plan cooperative activities in the cardiovascular area. During 1981, the Deputy Director, NHLBI visited the Hungarian Institute for Cardiology to continue this planning process. Plans are under way for exchanges of scientists for joint work.

Israel

In January 1980, the United States Department of Health and Human Services and the Israeli Ministry of Health signed a formal 5-year agreement for Cooperation in the Field of Health. Efforts are under way to develop further cooperative activities in areas related to the Institute's mission.

Cooperative epidemiological research with Israel to study determinants of cardiovascular disease has been funded by NHLBI grants and contracts for several years.

The population of Israel provides unique opportunities for epidemiological research. Jews have migrated there from many countries, and their diversity of lifestyles and genetic backgrounds constitutes a unique "population laboratory." Studies show that immigrants from different parts of the world have different plasma lipid distributions as well as variations in incidence and mortality of cardiovascular and other diseases. European immigrants came in the late 1940's, Yemenite Jews from Yemen, Iraq, Turkey, Iran, and Syria in the mid-1950's, and North African Jews in the mid-1960's. There is continual migration of Jews with a European background from North and South America and the U.S.S.R. While 90 percent of the youth are Israeli-born, only 20 percent of their parents were born there.

A multiethnic prevalence study, which is part of the Prevalence Study of the LRC program, is under way at the Jerusalem Lipid Research Clinic (LRC). All LRC clinics (nine in the U.S.A., one in Canada, one in Israel, and two in the U.S.S.R.) follow a standardized protocol. The aim of this network of clinics is to foster better diagnosis, management, and research in the area of hyperlipoproteinemias. The Israeli component of the Prevalence Study capitalizes on Jerusalem's unique population resource. Fifty-five countries of origin are represented in the Jerusalem study. This diverse population is divided into four broad groups according to country of origin (Israeli, Asian, North African, European/American). During 1980, the intake and screening of 8,609 17-year-olds was completed. Also, 6,984 of their male parents have been screened.

Preliminary results show important differences in dietary fat intake and blood lipid profiles which can be correlated with the country of paternal origin. Mean plasma high-density lipoprotein (HDL) cholesterol levels were highest among youths with fathers of European and American origin and lowest in those of Asian and North African descent. Second-generation Israelis ranked between the two groups. Total cholesterol levels were lowest in teenagers of North African descent, highest in youths of European and Israeli origin, and intermediate in those from Asia. Triglyceride levels were lowest among North Africans, but Asian and Israeli groups had higher values than the Europeans. Thus, patterns of lipid and lipoprotein levels previously observed in adult immigrants persist into a generation of native-born Israelis. Although ischemic heart disease incidence and mortality in Israeli ethnic groups correlated well with group mean total cholesterol values, the expected negative correlation with HDL cholesterol was not evident in the Asian and North African groups, which had the lowest HDL levels as well as the lowest incidence and mortality from heart disease.

The study also provides clues about the relative roles of genetic makeup and lifestyles in the etiology of cardiovascular disease. On first arriving, the Yemenites were thin and small in stature; they had no heart disease

or diabetes. After a single generation on an Israeli diet, however, they started to develop heart disease and diabetes but not to the extent of Israelis of European parentage. Another ethnic group, the Bedouin tribe, native to Israel, showed little or no cardiovascular disease, and men aged 60, 70, or 80 years had arteries similar to European children aged 3 to 4 years. This study is producing additional comparative data on national diets in the U.S.A. and Israel. The results of such strictly controlled international investigations can provide important clues as to whether lowering of blood cholesterol levels decreases heart attacks. A positive correlation could lead to the saving of many lives; a negative correlation could spare society the expense and social hardship of cholesterol-lowering diets and drugs. Medical information originating from the LRC international investigations will profoundly affect millions of lives in this and future generations.

The NHLBI also supports a joint American-Israeli Migrant Study of same-sex siblings, one of whom migrated to Israel and the other of whom remained in the U.S.A. Approximately 2,400 Israelis and 1,525 North Americans were given a complete physical examination to assess if differences in cardiovascular risk factors are influenced by genetic and/or environmental influences. Data analysis of this completed study is under way, and published reports are expected during FY 1982.

Italy

U.S.-Italian cooperation in the cardiovascular area was initiated in 1978 under the Joint U.S.-Italy Memorandum of Understanding signed by the Secretary, DHEW, and the Italian Minister of Health in Rome in November 1977. The purpose of these joint activities is to exchange, review, evaluate, and compare U.S. and Italian information in specific scientific areas judged to be of strong mutual interest and benefit and to develop scientist-to-scientist exchanges in these areas.

Three joint symposia have been held under the agreement. The proceedings of the first two have been published, and the third is in press.

Symposia on "Measurement and Control of Cardiovascular Risk Factors" and "Prostaglandins and Cardiovascular Disease" were held in 1978 and 1979. The methodology used for research on prostaglandins and cardiovascular diseases was examined, and the need was established for a better understanding of the role of prostaglandins in the normal functioning of the cardiovascular system and their possible involvement in certain disease states. Also, the mechanism of action of certain drugs requiring the presence of prostaglandins needs clarification, as do derivatives that may be potentially useful drugs.

A Joint U.S.-Italy Working Meeting on Methodology and Training in Prostaglandin Research in the Cardiovascular Area was held in May 1980. Problems were defined and common goals reviewed. The following three recommendations resulted: fullest support should be given to assay-method training programs which are broadly based and fully integrated, and these programs should be recognized as the principal areas

for exchange; deuterated standards of prostaglandins for gas chromatography and mass spectrometry should be made available at the national level, and to facilitate radioimmunoassay, the fullest characterization of antibodies and definition of their fields of application should be carried out; a working meeting should be held in 1982 to assess the results of joint U.S.-Italian efforts in this field.

The third joint symposium, "Nutrition and Cardiovascular Disease," held in December 1980, explored in depth the scientific questions relating to the role of nutrition in the development and prevention of cardiovascular disease. A wide range of subjects was considered. A major topic of the symposium was the role of nutrition in hypertension and its control. The U.S.-Italy Joint Steering Committee met in conjunction with the symposium. It reported that cooperative efforts were proceeding as planned and progress was good. The Fourth U.S.-Italy Joint Symposium, "Methods of Noninvasive Diagnosis in Cardiovascular Disease," to be held in the U.S.A. in November 1981, was planned. Topics to be discussed include: characteristics of atherosclerotic lesions as they pertain to noninvasive techniques; status of the technology and future trends; and validation of noninvasive techniques and the clinical applications of these techniques.

The first Fellow under the U.S.-Italy agreement worked for 3 months in the U.S.A. on the role of thromboxane in atherogenesis. She visited several U.S. laboratories to discuss work on platelet clotting, thromboxane, and atherogenesis. Cooperative research on platelets and sera from Tangier patients, who have a very rare genetic blood lipid abnormality, is under way. Platelet function testing will be carried out in Italy using the Fellow's unique assay system.

Joint studies are in progress to explore alternative methods to prevent and treat Hyaline Membrane Disease (HMD) and Adult Respiratory Distress Syndrome (ARDS). Pulmonary ventilation can be reduced or totally eliminated by using an extracorporeal membrane lung to remove metabolic carbon dioxide and using "apneic oxygenation" to deliver the oxygen necessary directly via the resting lung. NHLBI and Italian researchers are clinically testing a spiral blood coil gas exchanger on ARDS patients and on an animal model at high risk of developing HMD. During 1981, these researchers demonstrated that ARDS patients who met the criteria of 90 percent mortality can be placed on extracorporeal bypass for up to 2 days, allowing their lungs to heal sufficiently so that they can again breathe spontaneously. Similarly, when premature lambs which normally develop hyaline membrane disease are placed on this system for 2 to 6 hours postdelivery, they do not develop the disease. After this time, the lambs could be taken off the respiratory assist system, and their lung development proceeded normally. Collaboration with Italian researchers made human evaluation of this unique life-saving technique possible.

Japan

A U.S.-Japan Agreement in Science and Technology in Non-Energy Areas was signed in 1980 by the President

of the United States and the Prime Minister of Japan. The agreement, which includes collaboration in the area of cardiovascular diseases, is the result of a long and successful history of cooperative research between the two countries. A Japanese Coordinator for the cardiovascular area was appointed in 1981. Information exchange is under way, and specific themes and plans for the cooperation are in the developmental stage. U.S.-Japanese research on nutritional control of hypertension and its sequelae has been ongoing informally for more than 10 years, and both sides are interested in expanding these studies under the formal agreement. Other ongoing joint research involves studies on the comparative rates of coronary heart disease and stroke and genetic, nutritional, environmental, and other factors which account for differences in the health status of U.S. and Japanese populations.

Japanese scientists have made important contributions to the development of animal models for the study of hypertension. The development of the spontaneously hypertensive rat (SHR) at Kyoto University, and its use in animal research at the National Institutes of Health since 1969, led to ongoing collaboration between NHLBI intramural scientists and Japanese researchers. Significant differences in neurotransmitter metabolism were observed in these genetically hypertensive rats. In 1974, a substrain of the SHR, the stroke-prone SHR or SHR-SP, was developed in Japan. This substrain, which exhibits more severe hypertension than the SHR, was subsequently introduced into the NIH animal colonies. Extensive cooperative research, using these animal models of hypertension and stroke, has led to significant discoveries on the neuronal regulation of blood pressure, vascular structure, and the dietary factors that may influence the incidence of stroke in the SHR-SP.

SHR-SP animals fed the standard NIH rat diet had a considerably lower incidence of stroke than rats of the same strain fed the standard Japanese diet. Thus, SHR-SP receiving the Japanese diet evidenced more than 60-percent incidence of severe stroke by 10 months of age, whereas those receiving the NIH rat diet, though they developed hypertension, had only a 10-percent incidence of stroke. The major difference in the diets was the higher protein content of the NIH diet. It appears that the "stroke protection" is due to an increased intake of certain sulphur-containing amino acids and certain aromatic amino acids. To be effective, the dietary intervention must occur from the third through the sixth month of the rat's life (a period approximately equivalent to 15 to 20 years of age in man). Recent human epidemiological studies in Japan have confirmed the importance of dietary protein in the development of stroke. Other studies in the SHR-SP rats and in Japanese men have shown the importance of sodium/potassium (Na/K) ratio in the diet in the development of hypertension. Further studies are ongoing in man on the nutritional modulation of hypertension induced by high sodium intake. Also, the Japanese are testing a nutritional supplement rich in potassium chloride for use in borderline hypertensives. Japanese and U.S. workers have developed predictive tests for hypertension using red blood cell (RBC)

membrane properties. In young SHR's which have not yet developed hypertension, the RBC's show an increased permeability to sodium ions, lipophilic ions, and an increased osmotic fragility. Joint experiments are continuing to establish whether RBC membrane properties can provide an indicator of human susceptibility to hypertension before overt high blood pressure develops.

A joint publication on the nutritional prevention of stroke has been submitted for publication, and a joint project, *Experimental Studies and Dietary Prevention of Hypertension and Atherosclerotic Diseases*, is under way at NHLBI and in Japan. It is funded cooperatively by the National Science Foundation and the Japanese Society for Promotion of Science for 2 years (1981 and 1982). The Japanese workers have now also developed an arterio-lipodosis-prone rat (ALR) which provides a good model for studying atherosclerosis.

It is anticipated that the cooperative agreement between the U.S.A. and Japan will facilitate these important research efforts in hypertension and insure that scientifically validated results will be applied rapidly to the prevention, diagnosis, and treatment of hypertension, stroke, kidney failure, and atherosclerosis.

The Honolulu Heart Program, a long-term prospective study of coronary heart disease and stroke in 8,006 men of Japanese ancestry living in Hawaii, was started in 1970. The 10-year disease incidence and mortality roster has now been completed. Heart disease and mortality in this population were intermediate between the high levels of heart disease found in a similar cohort living on the U.S. mainland and the lower levels of one living in Japan. However, stroke prevalence was three times as great in the indigenous Japanese cohort than in the Honolulu cohort. There was a strong negative correlation between cancer, particularly colon cancer, and serum cholesterol levels in the Japanese cohort. The 10-year re-examination of 2,000 of these men is now under way and will be completed during 1982. The risk factors, both positive and negative, underlying these changes in morbidity and mortality trends are currently under study.

Kuwait

The United States-Kuwait Technical Cooperation Program in Health was signed May 1981. In March 1981, the Director, Kuwait National Health Planning Office, visited the NHLBI to explore programs in the prevention of cardiovascular disease. Kuwait is developing a National Health Plan and under the agreement is seeking consultant help to develop a National High Blood Pressure Education program. Like the U.S.A., Kuwait's major health problems are hypertension, cardiovascular disease, accidents, and other chronic diseases.

Nigeria

An Agreement for U.S.-Nigeria Cooperation in Biomedical Research was signed in September 1981 as a followup to the NIH-Nigerian Task Force meeting held earlier in that year. Nigeria shares with the U.S.A. such

chronic health problems as cardiovascular diseases and cancer. As the country undergoes major socioeconomic changes, these diseases are becoming more prevalent. Cooperative activities with the NHLBI are planned in the area of cardiovascular diseases, with special emphasis on hypertension and in the hemoglobinopathies, especially sickle cell anemia. Individual U.S. and Nigerian scientists are already undertaking research in epidemiology and hypertension control, and it is anticipated that these efforts will increase as lines of scientific communication continue to develop and strengthen between the two countries.

Senior scientists from several African countries (Sudan, Tanzania, Nigeria) who visited the NHLBI during FY 1981 showed a growing interest in carrying out cooperative projects in the area of hypertension. This disease is a common problem to the U.S. and African black populations. In the U.S.A., the disease is more prevalent and more severe among blacks. Hypertension appears to present different sequelae among the African black population, where there are fewer heart attacks and strokes associated with the disease than in the U.S.A. African hypertensives die more often from renal disease or cardiac failure. Furthermore, hypertension and other cardiovascular diseases such as rheumatic heart disease occur in a more telescoped timeframe in Nigeria than in the U.S. This provides a unique opportunity for joint studies to be done in a shorter timeframe than would be possible in the U.S.A. During FY 1981, several senior African scientists worked for extended periods in the United States to carry out hypertension-related research.

People's Republic of China (PRC)

An agreement between the Government of the United States of America and the Government of the People's Republic of China on Cooperation in Science and Technology was signed in January 1979. The subsequent U.S.-PRC Protocol for Cooperation in the Science and Technology of Medicine and Public Health in June 1979 identified cardiovascular disease as one of the seven areas of cooperation.

During 1979, the PRC coordinator visited the NHLBI for preliminary discussions. The Director, NHLBI, headed a five-member U.S. delegation for a reciprocal visit to the PRC in 1980. As a result, a proposed plan for U.S.-PRC Cooperation in the Cardiovascular Area was signed by the coordinators and approved by the respective governments. It was reported to the Joint Committee that "the U.S. and PRC sides have determined that one area, cardiovascular epidemiology, is by far the area of greatest mutual interest, mutual need, and mutual benefit to the peoples of both countries at this time."

The Chinese Coordinator for the Cardiovascular Area and the new Director for the National Cardiovascular Institute and FuWai Hospital in Beijing and three additional Chinese specialists visited in the United States in March 1981. A U.S.-PRC Joint Workshop on Arteriosclerosis and Hypertension was held, and plans for future cooperative activities were formulated. A four-member U.S. working group of car-

diovascular specialists visited China in April 1981 to initiate joint discussions of the planned U.S.-PRC studies of epidemiology of cardiovascular disease and the risk factors important in developing such disease. U.S. and Chinese scientists formulated a proposed joint U.S.-PRC protocol and discussed the standardization measurement techniques, collection of data, and analysis of joint data. It is anticipated that a final joint protocol will be presented to the U.S.-PRC Joint Health Committee at its Third Meeting in April 1982 in Washington.

In March 1981, two Chinese fellows commenced 12-month exchange visits to the U.S.A. to carry out joint research on the biochemistry of atherosclerosis and cellular studies of human atherosclerosis. Exchanges of information and scientists in the scientific areas designated for cooperation are expected to continue.

Poland

Exchange activities continued under the 1974 U.S.-Polish Agreement for Health Cooperation between the Department of Health and Human Services and the Ministry of Health and Social Welfare of the Polish People's Republic. A Joint Summary of Discussion was signed in March 1981 by the Director for Research Coordination of the National Institute of Cardiology, Warsaw, and the Director, National Heart, Lung, and Blood Institute, following a U.S.-Polish Symposium on Ischemic Heart Disease. The symposium covered a wide range of topics including: Epidemiology of Ischemic Heart Disease; Role of Prostaglandins in Ischemic Heart Disease; Prostacyclin and Atherosclerosis; Surgical Management of Ischemic Heart Disease; Noninvasive Diagnostic Techniques for Cardiovascular Disease; Technical Aspects of Endomyocardial Biopsy and its Value in Diagnosis of Cardiomyopathy; and Rehabilitation Following Acute Myocardial Infarction including the Psychological Indices of the Rehabilitation Process.

At a Colloquium on the Epidemiology of Cardiovascular Disease held in conjunction with the joint symposium, data were presented on cardiovascular mortality trends in the U.S.A. and Poland. The results of the pilot study for the U.S.-Poland Joint Study of the Prevalence of Lipid Metabolism Disturbances were also evaluated.

Simultaneously, a U.S.-Poland Steering Committee meeting took place to review activities carried out under the three areas previously agreed upon.

Area A. — Basic Research in Etiological Mechanisms. A U.S. scientist worked in Cracow for 2 months carrying out joint experiments on the endogenous production of Prostaglandin - G₂ and its metabolites. A Polish expert spent 2 months in the U.S.A. working in advanced lipoprotein research. He learned the latest U.S. techniques and commenced studies on apolipoproteins, which he is continuing in Poland.

Area B. — Clinical Research. A Polish physician worked in the U.S.A. on the diagnosis and treatment of cardiomyopathy and isotopic procedures for evaluating heart hemodynamics. A reciprocal visit to Poland by a U.S. physician is planned to carry out research on

noninvasive techniques in cardiovascular diagnosis and to learn endomyocardial biopsy techniques that have been successfully employed in Poland for the diagnosis of cardiomyopathy. A protocol for a collaborative study on the diagnosis and treatment of cardiomyopathy is under development.

Area C. — Epidemiological Research. A cooperative study, The Cardiovascular and Clinical Correlations of High Density Lipoproteins (HDL), is under development to explore the reasons for the marked differences in cardiovascular disease and risk factor trends in the U.S.A. and Poland. Cardiovascular death rates in the U.S.A. have decreased sharply, whereas these rates have increased in Poland. A Polish scientist visited the U.S. Lipid Research Clinics (LRC) to learn LRC techniques and procedures to be used in the joint study. A U.S. clinical chemist worked at the Departments of Metabolic Disease and Clinical Chemistry of the Institute of Medicine, Academy of Medicine, Cracow, to help initiate U.S. LRC procedures for blood cholesterol and triglyceride determinations. Standards, frozen sera, and quality control materials were supplied to the Polish side for use in the joint studies, allowing the Cracow laboratory to be standardized according to LRC procedures. In FY 1981, a U.S. epidemiologist and a biostatistician reviewed progress of the screening teams in Warsaw and Cracow. A small working group met to develop a protocol for a collaborative U.S.-Poland Study of Ischemic Heart Disease which would produce comparable valid data in the U.S.A. and Poland. The planned study will determine the prevalence of risk factors, ischemic heart disease, and risk of ischemic heart disease morbidity and mortality in middle-aged men comprising a subset of the Polish population selected from a planned WHO study.

A U.S. scientist visited Poland for joint review of the 3-year results of the Polish Trial in Multifactorial Prevention of Coronary Heart Disease. This trial, conducted under the U.S.-Polish Agreement, is part of a larger European study under WHO auspices. The study design calls for random allocation of pairs of factories for either intervention or control. The study population consists of 11 intervention factories with 9,115 subjects and 11 control factories with 8,120 subjects. Baseline findings from cardiovascular screening of 8,045 men in the intervention factories and 713 men (a 10-percent sample of the control group) have been published, as has a joint publication of recruitment data and initial findings from the Polish trial. The data are compared to those obtained in the United Kingdom, Belgium, Italy, and Spain. The Belgian study population was at highest risk of CHD; the Polish men, at lowest risk. Analysis of 3-year mortality data is under way from 6,000 men whose individual dietary intake data were recorded earlier. These dietary data will be analyzed for relationships to coronary heart disease and malignant neoplasms by a Polish mathematician who received 4 weeks of advanced statistical training at the Center for Disease Control plus an additional two weeks of training at the NHLBI.

Under the U.S.-Poland Collaborative Research Agreement, supported by the Marie Sklodowska-Curie

Fund, a Follow-up Study of Chronic Non-specific Respiratory Disease in Cracow continues. During FY 1981, two U.S. scientists visited Warsaw and Cracow to review progress. This study was first initiated in FY 1968, and 4,800 individuals (a randomized sample) from the Cracow population were studied. During 1973, 4,400 of the original study population were re-examined, and during 1981, approximately 3,500 of these individuals were re-examined for a third time. Standardized interviews and a medical exam which included lung function testing, sputum analysis, age, weight, and height measurements were carried out. This 13-year prospective study will yield important new scientific data on risk factors affecting the incidence, prevalence, and persistence of chronic nonspecific respiratory disease. No U.S. study of such duration exists, and it should supply further explanations of the natural history of this disease.

United Kingdom

Scientists from the NHLBI Division of Intramural Research continued their cooperation with British investigators in the development of a computer-based chemical information system (CIS). While the management for the CIS continues to be located in the NHLBI, funding during FY 1981 was drawn largely from the NIH management fund. The system includes analytical programs to accomplish iterative analysis of complex nuclear magnetic resonance (NMR) spectra, or general curve-fitting linear regression analysis, mathematical modeling, chemical synthesis programs, and many other specialized data bases. Utilizing joint efforts, the data bases for the system were assembled by the National Institutes of Health, the Mass Spectrometry Data Center (within the Department of Industry of the British Government), the Environmental Protection Agency, the National Bureau of Standards, and several other U.S. Government agencies as well as nongovernment U.S. units and groups from other nations. This valuable information system, which contains 30 specialized data bases, is being made available to scientists in North America and Europe by means of an international teleprocessing network. During FY 1981, 14 countries cooperated in the further development of the CIS: Australia, Finland, France, Germany, Holland, Hungary, Japan, Poland, Sweden, Switzerland, United Kingdom, the U.S.S.R., and Yugoslavia.

The British Norwegian Migrant Study surveyed by mail 73,884 men and women in the United States, Britain, and Norway to attain the prevalence of "angina" and other cardiorespiratory symptoms. The symptom of "angina" was reported more frequently by persons remaining in Britain and Norway than by the migrants to the U.S.A. During a 5-year period following the survey, angina was found to be a strong predictor of cardiovascular mortality. In the absence of angina, the migrants had a mortality rate similar to that of nonmigrants, regardless of country of origin. However, the British had higher mortality rates from cardiovascular and noncardiovascular causes than the Norwegians. The primary determinant of angina prevalence was found to be migration status. It is believed that those

who migrated constituted a healthier group than those who did not migrate.

The United Kingdom is one of the five countries undertaking the *European Trial in Multifactorial Prevention of Coronary Heart Disease*. The other countries, which use a common protocol and pool their data, are Belgium, Italy, Poland, and Spain. The United Kingdom study contains 24 factories with random allocation of pairs of factories to either a 6-year period of intervention efforts on risk factors or to control monitoring and followup of morbidity. Final enrollment was completed for all countries in 1977. The combined study consists of 63,732 men aged 40 to 59 years at entry and represents 88 factories. Followup is complete for the United Kingdom, Belgium, and Italy, and results are being published. Intervention achieved modest reduction of risk factors overall, and more substantial reductions were obtained in men at high risk.

U.S.S.R.

During FY 1981, cooperation between the National Heart, Lung, and Blood Institute and the U.S.S.R. Ministry of Health continued under the bilateral health agreement signed in 1972 and renewed in 1977 by the U.S. Secretary of State and the U.S.S.R. Minister of Health. Cooperation is proceeding in seven areas: Arteriosclerosis; Ischemic Heart Disease; Myocardial Metabolism; Congenital Heart Disease; Sudden Cardiac Death; Blood Transfusion, Blood Components, and Hepatitis; and Hypertension. Activities in these areas of joint cardiovascular research provide a constructive forum for interaction on problems of major national interest and need. The cooperative relationships established under this exchange provide a foundation of mutual respect and rapport which continues to yield scientific results of mutual benefit.

During the 9 years of cooperation, 502 specialists were exchanged in the seven cardiovascular areas for a total of 353 person-months. More than 100 U.S. and Soviet institutions have participated in the exchange, more than 60 in the U.S.A. and 40 in the U.S.S.R. Nineteen joint symposia have been held, and the proceedings have been published (or are being prepared for publication) in both English and Russian. Nearly 600 scientific reports, abstracts, and related articles have been published under the aegis of the exchange.

Area 1, Pathogenesis of Arteriosclerosis-The U.S.-U.S.S.R. collaboration in Area 1 provides a unique opportunity to study and compare the determinants and sequelae of coronary heart disease in different epidemiological settings. Both countries show a high incidence of heart disease, but differ significantly in ethnic and environmental characteristics. The highlight of cooperation during fiscal year 1981 was the *First Joint U.S.-U.S.S.R. Lipoprotein Symposium* held in Leningrad in May 1981. Presentations reported the results of 7 years of joint laboratory work and epidemiological studies on the prevalence of hyperlipoproteinemia and ischemic heart disease in Soviet and American populations. Further data were reported on correlates of

high-density lipoprotein (HDL) cholesterol. High levels of HDL cholesterol are associated with longevity, and this factor has been shown to be higher in Soviet populations than in comparative sample U.S. populations. Discussions focused on developing a basis for further U.S.-U.S.S.R. joint studies designed to explain the differences in HDL cholesterol levels among lipid research clinic (LRC) populations in the two countries, and to explore the potential for favorable modification of HDL cholesterol in populations. The cultural diversity of the studies, and the strong emphasis on the use of common procedures to collect data of comparable quality, increase the importance of the data and their ability to add to our understanding of heart disease.

One report, using multiple regression analyses, showed that in U.S. populations, 17 percent of HDL cholesterol could be statistically explained by behavioral characteristics, including alcohol intake and physical activity. The U.S. report corroborates conclusions of others that abstinence from cigarette smoking, a lean body, physical exercise, and moderate alcohol consumption are associated with increased level of HDL cholesterol, a condition regarded to be antiatherogenic. However, it is premature to infer a causal relationship between the above factors and HDL cholesterol levels. Proof of causality has to be reserved for future clinical and experimental studies. Nevertheless, the findings reported suggest the potential for favorable modification of population HDL cholesterol levels by hygienic means such as diet, exercise, and abstinence from cigarette smoking.

Papers also outlined the salient characteristics of the collaborative U.S.-U.S.S.R. study of the prevalence of dyslipoproteinemias, including an overview of the structure of the study, characteristics of the populations studied, and the common procedures utilized, such as plasma lipids and lipoprotein cholesterol determinations, as well as nutritional intake assessment and resting electrocardiography studies.

Comparisons of prevalence of ECG abnormalities and angina in comparative U.S. and U.S.S.R. male populations revealed that in both countries, the prevalence of ECG abnormalities and angina is higher for the 50-to 59-year age group than the 40-to 49-year age group. Also, the prevalence of angina is 3.3 times higher in the older groups compared to the younger groups. In both countries, people with ischemic heart disease had higher levels of total plasma cholesterol, triglyceride, LDL cholesterol, and systolic and diastolic blood pressure. Some of the differences may be related to the industrial location of the U.S.S.R. populations studied. The U.S. studies came from a variety of locations ranging from large cities to small rural towns.

In general, in the selected sample populations in both countries, the levels of plasma cholesterol and triglycerides are high. This is typical of developed countries with a high prevalence of ischemic heart disease. The analyses, based on common survey methods and highly standardized laboratory measurements, provide interesting contrasts in population distributions of lipids and lipoproteins in U.S. and U.S.S.R. middle-aged men. The implications of these

analyses are that plasma total cholesterol and HDL cholesterol levels are significantly higher, and triglyceride levels are significantly lower in the U.S.S.R. than in the U.S.A. Some of the differences observed in the distributions of these lipids and lipoprotein fractions may be attributable to environmental factors; some are likely to be attributable to genetic factors. The findings of distributional differences reinforce the importance of studying the relationship of these differences to various coronary heart disease risk factors and to the disease itself.

The above results represent the culmination of ongoing efforts by both sides to maintain good communication throughout the collaborative process, particularly through exchanges of individual scientists and working groups. A joint U.S.-U.S.S.R. Working Group meeting was held in conjunction with the symposium to discuss problems and review techniques to ensure the comparability of data gathered for the joint study. In Moscow, the working group reviewed the Followup Study and Prevalence Study data collection procedures and visited the ECG laboratory to observe ongoing exercise testing. In Leningrad, procedures in connection with the prevalence study were reviewed, and mortality classification procedures were discussed.

A Joint U.S.-U.S.S.R. Steering Committee meeting in Area 1 was held in conjunction with the symposium to review progress and develop plans for further activities. Both sides agreed to continue the exchange of epidemiologists and biochemists for individual studies and collaborative analysis of prevalence study data. Two areas were suggested for further data analysis and scientific publications: clinical chemistry data and blood pressure analysis. Plans are under way to gradually increase the proportion of basic research within Area 1. This is being initiated in parallel with the anticipated completion of the analysis phase of the epidemiological studies. Three basic research areas have been jointly agreed upon for continued collaborative work: cellular and lipid interactions at the arterial wall; structure and properties of lipoproteins; and platelets and lipoproteins.

Area 2, Management of Ischemic Heart Disease - During fiscal year 1981, joint cooperation in Area 2 focused on the *Second Joint U.S.-U.S.S.R. Symposium on Ischemic Heart Disease* held in Seattle, Washington, on March 20, 1981. Presentations at the symposium reported on patient-oriented research to find ways to minimize the mortality, morbidity, and suffering resulting from advanced coronary heart disease, including the results of ongoing studies in each country comparing different approaches to medical and surgical treatment of this disease.

One study reported on the use of ECG exercise testing in evaluating patients with ischemic heart disease. The results indicate that the ability of stress testing to predict coronary artery disease is limited in a heterogeneous population in which the prevalence of disease is estimated through classification of chest pain and the sex of the patient. However, probability curves derived from sophisticated statistical analysis on tread-

mill and angiographic data demonstrated that exercise testing provides more diagnostic information than clinical data alone in patients with definite and probable angina. Exercise testing in men with nonspecific chest pain was of limited value since disease prevalence was already low.

Another presentation reported on the procedure and results of an NIH consensus development conference on coronary artery bypass surgery. Evidence shows that an improvement in the quality of life, a decrease in myocardial ischemia, and an increase in survival have been demonstrated after coronary artery bypass in selected subsets of patients. Data presented at the symposium also indicate that coronary artery bypass surgery prolongs life in most patients with left main coronary artery (IMCA) disease, particularly those with severe IMCA narrowing or severe left ventricular dysfunction. However, subgroups of IMCA patients who fare well with medical treatment alone are identifiable. These results and others were discussed by the seven-member Soviet delegation and nine-member U.S. delegation participating in the symposium. The proceedings are being prepared for publication.

In conjunction with the symposium, a joint U.S.-U.S.S.R. working meeting was held to discuss the comparability of data in the joint clinical study to systematically assess and compare, in a well-defined group of cardiac patients, the relative effectiveness of the different treatment modalities used in the two countries. U.S. and Soviet angiographers read ventriculograms and angiograms with very good agreement between the independent readings. Comparisons were made of intake data and early survival experience. Subsequent to the symposium, the U.S. side received followup data which are being entered in the Data Coordinating Center in Seattle for computer analysis.

In addition to participating in the Second Joint Symposium, the Soviet scientists attended the 30th Annual Scientific Session of the American College of Cardiology in San Francisco. They visited laboratories in Palo Alto, California, and in Birmingham, Alabama, where mutual interest was expressed in the following themes: the role of spasm in ischemic heart disease; circulatory insufficiency in ischemic heart disease; the role of thrombocytes and blood coagulation in ischemic heart disease; hypertensive heart disease; and issues of angiography. Future U.S.-U.S.S.R. cooperation will build on these areas of mutual interest.

Prior to the symposium, a five-member U.S. delegation visited the U.S.S.R. in October 1980 to review progress on the joint studies, to discuss data analysis techniques, and to develop criteria for interpretation of results. The U.S. delegation visited laboratories and scientific institutions in Moscow, Kaunas, Vilnius, and Tashkent. Problems of reference group comparability were resolved, and a schedule for transmission of followup data developed.

Further plans include continued monitoring of patients up to June 1983. Followup data are to be forwarded to the Data Coordinating Center through the U.S. Coordinator twice a year for the third, fourth, and fifth years of followup; and some of the U.S.S.R. data

are to be analyzed as both data in the reference group and in the intensive treatment group. Also, a joint working meeting is planned for 1982 in Moscow. Both sides acknowledged interest in further collaborative studies on ischemic heart disease.

Area 3, Myocardial Metabolism-Joint cooperation in Area 3 incorporates a number of basic research projects. These are aimed at the discovery of new information that may help in the development of improved methods for prevention and treatment of cardiac disease. Current studies focus on the manner in which heart muscle cells obtain energy, regulate their growth, coordinate their contractions, and respond to alterations in their environment. Accordingly, presentations at the *Fifth Joint U.S.-U.S.S.R. Symposium on Myocardial Metabolism*, which was held in June 1981 in Hershey, Pennsylvania, were organized to report the results of joint studies in each of the above areas.

One symposium presentation reported on the results of a joint study by U.S. and U.S.S.R. scientists on energy channelling by heart creatine kinase, particularly the influence of oxidative phosphorylation on the kinetics of the reaction. The success of this highly specialized joint work derives from the complementary skills of the U.S. and U.S.S.R. cooperating scientists.

Studies to elucidate the microprocesses involved in normal heart function and their modification in damaged heart muscle were also reported jointly by U.S. and U.S.S.R. scientists. These include studies of the energetics of heart muscle contraction and relaxation, particularly the role of cyclic nucleotides in these processes. Calcium transport by the cardiac sarcoplasmic reticulum is being investigated to define more accurately the functions of this important cell component. Joint experiments are also under way to define the immunological properties of calcium ATPase of the cardiac and skeletal muscles.

U.S. and U.S.S.R. scientists also reported on the development of new methods to evaluate the hormone receptor apparatus in cells. Joint studies are under way on the mechanisms by which glucocorticoid and thyroid hormones potentiate the effect of catecholamines and how these hormones produce functional changes of the membranes surrounding the various intracellular organelles.

These projects are indicative of the various approaches taken by cooperating scientists to investigate normal heart function as well as the disruptions of the biochemical and biophysical processes that result from a heart attack. Some effects of myocardial infarction are reversible; others are not. One of the major thrusts of research in this area is determining with greater precision the exact point of irreversible cell damage so that therapies may be designed accordingly.

The U.S. side plans to publish the Proceedings of the Fifth Joint Symposium on Myocardial Metabolism as a supplement to an international scientific journal. The Soviet side will publish the proceedings in Russian.

For the future, exchanges of scientists will continue for experimental work to assess and limit the extent of heart muscle damage following myocardial infarction, including studies of amino acid metabolism, protein

turnover, and nitrogen metabolism in heart muscle as well as joint research on new approaches for targeting drugs to damaged heart tissue.

Area 4, Congenital Heart Disease-Congenital heart disease is an important cause of premature death and can significantly impair the quality of life from childhood to adulthood. The objectives of U.S.-U.S.S.R. collaboration in Area 4 are to explore new methods of diagnosis and postoperative care to reduce mortality from congenital heart disease and to improve the surgical treatment of complex heart defects. Cooperation has focused primarily on the holding of joint symposia and exchanges of working groups, delegations, and individual surgeons and physicians.

In followup to the *Fourth Joint U.S.-U.S.S.R. Symposium on Congenital Heart Disease* held in September 1980 in Moscow, the U.S. and U.S.S.R. chairmen met in May 1981 with the NHLBI staff in Bethesda to discuss progress and plans in joint cooperative activities on the diagnosis, treatment, and surgical repair of congenital malformations of the cardiovascular system. As a result of the meeting, it was agreed that further exchanges of scientists would be fruitful in the following areas: the study of cardiac function and the blood circulation system utilizing mathematical models following open heart surgery; the study of valvular grafts in children up to 14 years of age; the study of possible surgical treatment of rare forms of cardiac arrhythmias; the study of severe forms of pulmonary hypertension in children up to age 10; and the study of emergency surgery for newborn infants and those in the first 3 years of life who have congenital heart defects.

In addition to the joint working meeting, the visit of the U.S.S.R. chairman and his deputy included discussions with U.S. surgeons attending the meeting of the American Society for Thoracic Surgery in Washington, D.C. Followup observations of surgery at Duke University Medical Center, Durham, North Carolina, the University of California in San Francisco, and the Children's Hospital Medical Center in Boston led to the exchange of information on methods to insure safety during operations; development of new types of operations; prevention of complications during operations and in the postoperative period; and programming for experimental and computer analysis of patient followup and treatment.

Area 5, Sudden Death-Sudden cardiac death claims the life of one American every minute. It constitutes the leading cause of death in the U.S.A., as well as in other industrialized nations. In the U.S.A., 50 percent of all deaths from coronary heart disease occur suddenly. The immediate mechanism of sudden death is believed to be a disturbance in heart rhythm.

The goal of scientific collaboration in Area 5 is to learn more about the mechanisms of arrhythmias and precisely how antiarrhythmic agents intervene to normalize the heart's electrophysiologic functions. Joint cooperation focuses on the pathological anatomy and electrophysiology which may lead to sudden cardiac death, and the pharmacology of possible prophylactic antiarrhythmic drugs. Six topics have been designated for scientific exchange in Area 5: pathologic-

al anatomy, electrophysiology of sudden death; study of the effects of antiarrhythmic drugs; clinical aspects of sudden death; epidemiology of sudden death; and higher nervous and peripheral nervous activity in ventricular arrhythmias and sudden death.

Future plans in Area 5 include a U.S.S.R. Working Group visit to the U.S.A. in late 1981, in anticipation of the Third Joint Working Symposium to be held in 1982 in Kaunas, Lithuania. The symposium will be held in conjunction with the International Congress of Cardiology to be hosted by the Soviet Union in June. The U.S. delegation will be reviewing ongoing USSR studies at research centers in Riga, Tallin, and Leningrad.

Area 6, Blood Transfusion-U.S.-U.S.S.R. cooperation in Area 6 is concerned with research on the preservation and use of blood and blood products in cardiovascular surgery, focusing primarily on the problems associated with hepatitis, posttransfusion hematologic complications, and blood substitutes. Also, in the recent past, the U.S. and U.S.S.R. Working Programs in Area 6 have gradually developed an interest in joint cooperation on thrombosis and hemostasis, with particular emphasis on hemophilia and other genetic bleeding disorders, and on platelet abnormalities. A delegation of four U.S.S.R. scientists visited the U.S.A. in November 1980 for discussions of blood-transfusion-related research, including the role of platelet-vascular wall interaction in homeostasis, and the importance of thrombin and plasmin generation in the disseminated intravascular blood coagulation syndrome. These discussions led to an exchange of methodologies on blood separation and to the development of plans for continued cooperation.

A five-member working group visited the Soviet Union in May 1981 to investigate the treatment and management of patients with abnormal hemostatic mechanisms and to examine physiologic and pathologic alterations of the blood-vascular system as a result of transfusion. In addition, proposals were discussed for the exchange of specialists in the areas of preservation of platelets and red cells, blood substitutes, the prevention of hepatitis, and the use of blood and blood products. The U.S. investigators visited scientific centers in Moscow and Leningrad and also the Institute of Hematology and Blood Transfusion in Tbilisi. Sites visited in Moscow included the Blood Transfusion Division, the Laboratories of Cryopreservation, Gravitation Surgery, Pathophysiology, and the Hemophilia Center in the Central Institute of Hematology and Blood Transfusion. As a result of joint discussions, potential cooperative projects were outlined in hemophilia, plasmapheresis, blood component preservation, and the mechanisms of thrombohemorrhagic complications during massive transfusions.

In conjunction with the working group meeting, two U.S. exchange scientists visited the Soviet Union to present lectures and conduct joint discussions with Soviet counterpart specialists. One of the scientists discussed topics in blood transfusion therapy with special emphasis on the application of electron microscopy to the problem of platelet morphology. The other scientist focused on the storage of blood components

and on donor risks relative to blood separation technology and the use of chemical agents for the separation of blood components. She also presented an overview of the application of plasma exchange in a variety of medical conditions and discussed the collection and transfusion of blood components such as granulocytes, platelets, and mononuclear cells.

Plans for further collaboration include the following activities: continued exchanges of scientists for research on blood substitutes, posttransfusion hepatitis and plasmapheresis; development of preliminary cooperative protocols for projects of mutual interest designed to allow a comparison of U.S. and U.S.S.R. results and data; continued exchange of reagents and reference preparations as may be required in jointly approved protocols and to compare laboratory methodologies; development of joint publications on cooperative studies; exchange of delegations to monitor progress of collaborative activities and to review the status of research; and development of plans for a Third U.S.-U.S.S.R. Joint Symposium in Moscow, in 1983.

Area 7, Hypertension-The Joint U.S.-U.S.S.R. Symposium on Biobehavioral and Epidemiological Aspects of Hypertension, held in May 1981 in Bethesda, was the focus for cooperative activity between U.S. and Soviet scientists working to learn more about the prevalence, causes, treatment, and prevention of this "silent killer."

One U.S. paper reported evidence that certain animals, by virtue of their genotype, exhibit unusually pronounced cardiovascular reactions to stressful stimuli. Additionally, evidence derived from animal models indicates that chronic exposure to a stressful environment can profoundly affect the ultimate level of blood pressure, but only in animals with a genetic predisposition to hypertension. These data suggest that genetic factors must be assessed and accounted for when examining the importance of psychological influences in the pathogenesis of hypertension.

Another paper reported on population studies of U.S. and U.S.S.R. individuals with categorically defined diastolic hypertension who did not have blood pressure levels controlled below 95mm Hg at the time of the studies in 1972-76. Average followup of 4 years duration disclosed a sizable gradient of increasing cardiovascular disease mortality in relation to blood pressure levels within the range traditionally considered high-normal, or slightly elevated. These observational survey findings cannot address the causal nature of the relationships. However, they do suggest potential for either primary prevention or modification of extant elevated blood pressure by hygienic measures, and furthermore, suggest that a measureable impact on mortality might result from interventions of this type. They also provide justification for further collaborative lifestyle interventional research designed to lower morbidity and mortality, and suggest the importance of further developing nonpharmacological approaches to the prevention and treatment of hypertension.

Reports by both sides also emphasized the need to know more about the role of the nervous system in cardiovascular disease, to gain a better understanding of the neural pathways that influence cardiovascular

function. Soviet work on hypertension supports the view that hypertension results from changes in central nervous system functions produced by conflict situations, and, among the various operations which can be effective in inducing these conflict states are: immobilization, constant irregular harmful stimulation, and significant, lengthy anticipation of harmful event. Where Soviet research emphasizes the search for the central nervous system structures involved in the peripheral adaptations, U.S. studies tend to focus on functional relationships between environmental factors and subsequent long-term circulatory adaptations.

Following the symposium, a Soviet specialist visited U.S. scientific centers including the NHLBI, the National Institute on Aging in Baltimore, Maryland, and the Regional Primate Research Center of the University of Washington, Seattle, for discussions with U.S. scientists on the neurophysiological mechanisms of emotional stress in experimental animals. The NHLBI Chief of the Behavioral Studies Branch visited the Soviet Union in September 1981 for discussions of joint biobehavioral activities during the coming year.

Future plans include a visit to the U.S.S.R. by a U.S. working group in 1982 to assess problems of definition and classification of hypertension; examine the clinical, basic science, and epidemiological aspects of the relationship between salt and hypertension; review population studies on hypertension control; and discuss behavioral approaches to hypertension treatment.

U.S.-U.S.S.R. Cooperation on Artificial Heart Research and Development

Scientists in both the U.S.A. and U.S.S.R. recognize that present and foreseeable techniques of surgical and pharmacological management of acute chronic heart failure and shock still leave a substantial fraction of patients with compromised or fatally impaired heart function. Supportive mechanical devices can assume some of the pumping function of the heart and relieve its workload. Mutual interest in the development of better technology for mechanically assisted circulation resulted in 1974 in the Joint Agreement between the Government of the U.S.A. and the Government of the U.S.S.R. on Cooperation in Artificial Heart Research and Development. The Agreement was renewed in 1977 for 5 years. Since 1974, 58 specialists have been exchanged in this area for a total of 31 person-months. Two joint symposia have been held. The proceedings of the First Joint Symposium on Mechanically Assisted Circulation and the Artificial Heart have been published in English by the U.S. side, and in Russian by the U.S.S.R. side.

During the past year, joint activities in the area focused on the Second Joint U.S.-U.S.S.R. Symposium on Mechanically Assisted Circulation and the Artificial Heart held in Houston, Texas, September 22-29, 1981. Soviet research papers discussed the prospective use of implanted circulatory assist systems and artificial hearts with a radioisotopic power source; the development of methods of circulatory assistance and artificial heart

ventricles; and numerical modeling of the blood flow in the ventricular cavity of the artificial heart. U.S. presentations reviewed the status of implantable energy systems to actuate and control ventricular assist devices; new mechanical techniques of circulatory support; and electrical energy converters for practical human total artificial hearts. One paper outlined the major components of an implantable ventricular assist device including 1) energy source, 2) energy transmission, 3) energy storage, 4) energy converter, 5) blood pump actuator/controller, and 6) blood pump. The challenge of an integrated left ventricular assist system (LVAS) is a design that is capable of supporting the full cardiac output required for the patient. Developing an energy system to actuate a permanent implantable left heart assist or total heart replacement device must take into account the following factors: selection of a source of energy to provide mobility; selection of the appropriate energy conversion technique to translate the energy from the source to that form required to actuate the blood pump; and definition of methods to control the blood pump to meet variable physiological needs. Through joint collaboration, U.S. and Soviet scientists are sharing their knowledge and laboratory experience to advance progress in meeting these challenges.

Discussion for further joint activities reviewed the accomplishments of a three-member delegation visiting the U.S.A. in August 1981 for joint *in vitro* and *in vivo* testing of a Soviet control system received in the U.S.A. in July. In conjunction with this visit, U.S. and Soviet scientists also developed a potential joint collaborative project on biomaterials. The joint project relates to the U.S.S.R. symposium presentation "A system of tests for assessing hemocompatible properties of polymer materials," and involves characterization of the absorption of human albumin to three or four well-characterized materials. The primary goals are to understand better the basic mechanisms of blood-material interactions and to assess the comparability among laboratories of experimental results. Followup arrangements for exchanges of materials and experimental results are in progress.

Plans for further joint activities include the development of joint publications, exchanges of various device components by the two sides, and continued exchanges of scientists in the following areas: intra-aortic balloons, left ventricular assist devices, artificial hearts, biomaterials, and *in vitro* evaluation.

Venezuela

A joint U.S.-Venezuela Agreement for Scientific and Technological Cooperation in Health was signed in August 1980, and discussions are under way to implement cooperative efforts under this agreement. Venezuelan scientists have a strong interest in cooperation in the cardiovascular area, focusing on clinical research. Possible collaborative efforts in the area of Chagas' disease are being investigated. Venezuelan and NHLBI investigators are developing a protocol which could provide a human model of cardiopathy, to prospectively study this disease.

Yugoslavia

An agreement between the United States and Yugoslavia was signed in May 1973 to encourage research projects of mutual interest, utilizing P.L. 480 funds. The NHLBI and Yugoslav investigators from the Institute of Chronic Diseases and Gerontology are continuing the long-term prospective study of the epidemiology of cardiovascular disease in a large population of Yugoslav men. From its inception in Bosnia in 1962, personnel from the Framingham Massachusetts study were involved, so that data from this study are statistically comparable with the Framingham data. The Yugoslav study examined 11,121 men aged 36 to 62 years over a period of 7 years and is attempting to relate changes in trends of coronary heart disease (CHD) risk factors and the prevalence of CHD death to changes in the sociocultural environment. Both the urban and rural cohorts examined had serum cholesterol levels well below the typical U.S. population of Framingham, and the Yugoslav incidence of CHD appears to be one-fourth that in the U.S.A. Repeat measurements taken 7 years later showed increases in the average diastolic and systolic pressures and increases in the prevalence of high blood pressure. Increases were greater in the rural than in the urban settings. The Yugoslav population also showed a significant weight increase during the 7-year period. Correlation of deaths from CHD and serum cholesterol levels were positive. However, mortality from all causes increased at the lower serum cholesterol levels. The increased deaths in people with very low serum cholesterol levels were the result of increased respiratory disease deaths, and to lesser extent, an increase in the cancer death rate. This study is now completed, but combined data analysis continues. Six joint publications have resulted to date, and study data were presented at the 1980 meeting of the American Heart Association Council on Epidemiology, the NHLBI Workshop on Cholesterol, and the European College of Cardiology in Paris.

The same group of investigators is now beginning a new joint project--An Epidemiological Study of Secular Trends in CHD Risk Factors in Yugoslavia--which is a logical continuation of the previous study. It will attempt to answer specific questions that arose during the data analysis phase of the earlier study. New cohorts of Yugoslavs aged 35 to 64 years will be followed to evaluate changes that have occurred in the next generation. Cohorts from both the industrial areas and the rural areas of Belgrade and from Tuzla, a recently industrialized city, are being examined. In April 1981, a U.S. epidemiologist helped develop the survey questionnaire, and during September 1981, two U.S. scientists visited the study sites to finalize pilot study plans. Parameters to be measured include total cholesterol, high-density cholesterol, triglycerides, and serum glucose. Standardization of the biochemical parameters will be carried out and monitored with the help of the Center for Disease Control (CDC), Atlanta. As a result, valid data comparisons from this study with U.S.- and WHO-sponsored epidemiological studies will be possible.

Activities with International Organizations

World Health Organization

In FY 1980, the Institute was designated by the World Health Organization (WHO) as its Regional Collaborative Center for Research and Training in Cardiovascular Diseases for the Americas. In this capacity, it provides advisory services for WHO and collects and exchanges information on cardiovascular diseases. Data pertaining to all facets of disease control, from basic research results to epidemiological studies, and data from prevention and control activities form part of this exchange. The Director, NHLBI, served as an advisor to WHO in the area of long-range planning in cardiovascular disease.

Data from the ongoing U.S. Coronary Artery Surgery Study (CASS) continued to be exchanged with the participants of the European Coronary Artery Study coordinated by WHO. Collaboration among CASS, the Veterans Administration Coronary Artery Surgery Study, and the European Study continued as planned. An expert consultant identified by the NHLBI assisted Thailand in its WHO-sponsored national planning effort in the cardiovascular area. The recommendations of this senior U.S. scientist were approved by the National Committee on Prevention and Control of Cardiovascular Disease in Thailand for implementation within that country's national program. A cardiovascular epidemiologist was identified to assist India in a WHO-sponsored national planning effort for future programs in the cardiovascular area. Similarly, the NHLBI identified an expert to aid Bangladesh in its development of a cardiovascular disease control program. Using its extensive knowledge of risk factors for cardiovascular disease, the NHLBI continues to be involved in establishing comprehensive WHO programs for the nonpharmacological prevention and control of chronic noncommunicable diseases. Pilot studies in selected communities are now under way in the WHO-sponsored program, *Multinational Monitoring of Trends and Determinants in Cardiovascular Disease*. Data from this state-of-the-art study will provide a more accurate assessment of trends in heart disease morbidity and mortality within and between countries.

Commission of European Communities

The NHLBI is cooperating with the Commission of European Communities (CEC) in the area of extracorporeal oxygenation. Institute staff are working with the European Concerted Action on Extracorporeal Oxygenation (ECAEO) to exchange information about ongoing research on how to "transplant" the most up-to-date developments in engineering design, coagulation problems, and control systems as they relate to long-term respiratory support therapy. The

Director, Division of Blood Diseases and Blood Resources, met with the Coordinator for the CEC's "Concerted Action on Detection of the Tendency to Thrombosis" to exchange information. The European countries participating in this project are Denmark, France, The Netherlands, the United Kingdom, and the Federal Republic of Germany. Information has been exchanged regarding the CEC Concerted Action on Common Standards for Quantitative Electrocardiography. Researchers from the U.S.A., Canada, and Japan, as well as researchers from CEC countries, have collaborated to develop the protocol for this study. Members of the working group for this project consulted with NHLBI staff. The Institute also provided input to the International Bone Marrow Transplant Registry organized by the CEC.

International Visitors and Meetings

Joint research was carried out in laboratories of the Division of Intramural Research by 75 international investigators. They came from Argentina, Canada, the Federal Republic of Germany, France, Italy, Japan, The Netherlands, Poland, Sweden, Turkey, and the United Kingdom. Many foreign scientists participated in the Seventh U.S. National Conference on High Blood Pressure Control as well as several state-of-the-art workshops and consensus-development symposia organized by NHLBI during FY 1981.

Extramural Programs

During FY 1981, the NHLBI awarded 17 contracts and eight grants to the following foreign countries: Argentina, Australia, Canada, Denmark, Israel, Italy, Romania, and Sweden. They supported mainly cooperative epidemiological studies or foreign components of national clinical trials. Seven fellowships were awarded U.S. to scientists for training in the following countries: Belgium, Canada, Denmark, the Federal Republic of Germany, Israel, and the United Kingdom.

In one study, the effect of migration on the familial aggregation of blood pressure on Tokelau Islanders who migrated from an atoll in the South Pacific to New Zealand was investigated. This collaborative multidisciplinary study is focusing on the changes in blood pressure and other variables important in cardiovascular disease. The study is unique in that the population was surveyed before migration was completed and that both the nonmigrant population (in Tokelau) and the migrant population (in New Zealand) are subject to longitudinal followup. Migrants showed a considerable increase in the prevalence of hypertension and a less marked increase in mean blood pressure. Obesity, which is increased in the migrants, is clearly a factor in their elevated blood pressure.

NATIONAL INSTITUTE ON AGING

Introduction

Between now and the year 2000, the segment of the population that is 60 years old or older will grow faster than any other age group in both the developed and developing world. Considerations surrounding this demographic development have prompted the community of nations to convene the United Nations World Assembly on Aging (UNWAA) to be held at the Hofburg Palace in Vienna from July 25 to August 6, 1982. The agenda for the conference includes health as a primary humanitarian issue for consideration. Collaborative efforts are under way to extend the mandate of the National Institute of Aging (NIA) beyond the borders of the United States in drafting, with the World Health Organization, a program of action for the UNWAA. The goals of the program would include a coordinated research and development program to increase the independence of older people and their contribution to society and to promote health maintenance and well-being of the elderly.

Planning and priority-setting in developing a global program must depend upon evolution in specific areas, including health costs, epidemiology, the burden of illness, the avoidance of trivial or duplicative research, the state of the art, and the availability of resources.

Summary of Bid International Programs and Activities

Cooperation with International Agencies - World Health Organization

The Institute's association with the World Health Organization (WHO) was formalized in the May 1981 designation as the first WHO Collaborating Center for Joint Cooperation on Research on the Care of the Aged. Under the terms of the agreement, both WHO and NIA would be involved in the followup of the December 1980 WHO Preparatory Conference for the World Assembly on Aging in Mexico City, for which the Institute provided financial and planning support.

The major themes of the Conference were based on the WHO strategies of Health for All by the Year 2000, Services and Technology, Intersectoral Cooperation, and Program of Future Action. Recommendations for the WHO Global Programme for Care of the Aged were offered. Research on the problems of the aging, and

particularly health services research, were considered of the highest priority.

In July 1981, the NIA Associate Director for Epidemiology, Demography, and Biometry chaired the WHO Workshop on Policy Oriented Research on Health Care of the Elderly. This workshop dealt primarily with population-based health and social research. The recommendations will be used in the preparation of documents for the 1982 United Nations World Assembly on Aging.

The fifth WHO-sponsored meeting of directors of national institutes of gerontology hosted by the NIA is planned for The White House Conference on Aging in November/December 1981. Representatives from the following member nations will be invited: Senegal, Brazil, Costa Rica, Venezuela, India, Israel, France, German Democratic Republic, Hungary, The Netherlands, Norway, Romania, Sweden, United Kingdom, Union of Soviet Socialist Republics, Australia, Japan, and the People's Republic of China.

Extramural Program

Eight grants to foreign investigators, or involving studies of societies, cultures, or groups in other regions of the world, were funded by the Institute during FY 1981. Support for these multiyear awards totalled about \$632,869, and represented slightly over 1 percent of the total FY 1981 NIA extramural support program, as opposed to less than 1 percent in preceding years.

The versatility of the areas being supported is in keeping with the multidisciplinary nature of the Institute's biomedical and behavioral sciences programs. Some projects are: basic studies on defective enzymes in aged animals by an investigator at the Israel Institute of Technology; testing in Belgium of a genetic developmental theory of aging at the level of the species, using *Drosophila melanogaster*; retirement and aging in cross-cultural perspective involving situations of older people in China, Russia, and several Eastern European countries; and studies of adult twins reared apart in Sweden and Finland to learn about aging changes in cognitive and noncognitive domains.

Conferences, Seminars, and Meetings

In May 1981, the Institute, in cooperation with its National Advisory Council on Aging, held a Seminar on International Developments in Aging to inform the Council members, staff, and guests of the global

concerns and activities that bear upon the "greying of nations," to facilitate exchanges among the key organizations, and to consider health-related research as a vital part of the 1982 United Nations World Assembly on Aging. Guest speakers included the Chairman of the WHO Global Advisory Committee on Medical Research; the Chairman of the Subcommittee of Health and Behavior of the Global Committee; Director, Programme Management, WHO Regional Office, Europe; Deputy Director, WHO Office of the Americas (PAHO); and the U.S. State Department Coordinator for the 1982 U.N. World Assembly on Aging.

The following seminars were conducted during the last year:

- High Altitude Research, Cayetano Heredia University, Lima, Peru
- Intracranial Self Stimulation of an Anti-Stress Factor, Anochin Research Institute and First Moscow Medical School, U.S.S.R.
- Models of Cardiac Hypertrophy, Universität Tubingen, Germany
- Mechanism of Action of Glucagon in Liver Mitochondria, Nencki Institute of Experimental Biology, Warsaw, Poland
- Photocoustic Spectroscopy, Hyderabad, India
- Cardiovascular and Behavioral Interactions, Köln University, Germany

Intramural Programs and Activities Including NIH Visiting Program

The Intramural Research Program of the National Institute on Aging is conducted at the Gerontology Research Center located in Baltimore, Maryland. During fiscal year 1981, the Center's international activities involved research training for 33 Visiting Scientists, Fellows, and Associates from 15 countries: Australia, Canada, Chile, Egypt, Finland, Greece, Hungary, India, Israel, Italy, Japan, Poland, Sweden, Taiwan, and Turkey. The foreign nationals worked in the NIA laboratories, where investigators conduct quantitative and qualitative research into many of the biological, physiological, medical, and behavioral factors associated with animals, including humans.

In addition to the geriatric research training opportunities afforded within the NIA intramural program, the GRC hosted visits by international delegations such as members of the Georgian Academy of Sciences, U.S.S.R., who conferred with GRC staff on human aging studies conducted in this country and exchanged ideas about such studies in their respective countries. This Soviet visit was sponsored by the U.S.-based Institute for the Study of Man.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

Introduction

The National Institute of Allergy and Infectious Diseases was formally established by law in 1948 as the National Microbiological Institute. Its change of name in 1955 reflected the increased emphasis on basic research in communicable diseases and immunological disorders. Following the dissolution of the NIH Office of International Research in 1968, NIAID assumed the major responsibility for tropical medicine activities. Intramural research is carried out by approximately 600 staff members in Bethesda, Maryland, and the Rocky Mountain facilities in Hamilton, Montana. The NIAID extramural research program, however, constituted more than 80 percent of the total budget in FY 1981. Academic and research institutions carry out these extramural activities through research and training grants and contracts.

Infectious diseases continue to be the most frequent reason for patients to seek medical attention in industrialized societies, and they are still the leading cause of reported morbidity and mortality in developing countries. The results of the domestic NIAID program, therefore, have inherent and far-reaching relevance for national health authorities outside the United States and for agencies that cooperate with them in applying this new knowledge and technology to disease prevention and control.

During FY 1981, NIAID continued to assign special priority in its Tropical Medicine Program to filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis. These are the six diseases targeted for intensive research by the WHO/UNDP/World Bank Special Program on Tropical Disease Research (TDR). Reporting these tropical diseases separately facilitates communication and coordination with WHO and other international agencies. The NIAID Tropical Medicine Program also includes other infectious diseases in which international collaboration is essential to complement the domestic research effort. These activities are discussed in this report under general parasitology; tropical bacteriology, mycology, and virology; rickettsioses and vector pathogens. Additional conditions that constitute more serious public health problems in developing countries than in the United States are the subject of international collaboration but are not included in the budgetary figures for the Tropical Medicine Program. Examples include: gastroenteritis

other than cholera, hepatitis, acute respiratory illness, and sexually transmitted diseases.

General parasitology consists of research on the remaining parasites of importance to human health and basic research projects, parasitology research training, and career development awards which could not be assigned to any one of the six targeted diseases. Basic research in parasitology is a prerequisite to further understanding and advances in the prevention or control of the five parasitic diseases of TDR. Indeed, the disease-oriented initiatives of the Public Health Service (PHS), Army, Navy, USAID, and WHO have evolved from and will continue to rely on basic research breakthroughs to achieve their goals of vaccine and drug development or vector control.

During FY 1981, tropical bacteriology awards (7 percent) were heavily concentrated in research on cholera and related organisms (12), tuberculosis and mycobacteria other than leprosy (4), leptospirosis (1), nonvenereal treponematoses (1) and yersinia (1). Although WHO has recently established a Global Diarrheal Disease Control Program (DDC) with a major research component in epidemiology, improved drugs, and vaccine development, NIAID activities in viral and bacterial diarrheas other than cholera are not a formal part of the Tropical Medicine Program.

Histoplasmosis (5) and coccidioidomycosis (2) contribute the bulk of the tropical mycology area (2 percent). The rickettsiae program (3.7 percent) is directed primarily toward Rocky Mountain Spotted Fever. Tropical virology (8.4 percent) includes 21 research projects in arboviruses (12), rabies, and other viral agents of public health importance (e.g., Lassa fever) which are not endemic to the U.S.A. Vector pathogen activities (7.4 percent), by contrast, consisted of 26 projects to study the mosquito (14), fly (2), tick (2), mite (1), and snail (4) vectors of human viral, rickettsial, and trematode diseases.

Foreign investigators are eligible to compete with U.S. investigators for NIAID grants and, under special conditions, for "sole resource" contract funds. The bulk of NIAID-sponsored international research, however, is generated through NIH awards to U.S.-based scientists and institutions. NIAID grants for International Collaboration in Infectious Diseases Research (ICIDR) are intended to provide such a linkage for research to be done outside the country. The ICIDR program, as well as the NIAID-supported Tropical

Disease Research Units (TDU) within the United States, will be discussed later in more detail. Additional mechanisms include bilateral medical research programs and the Special Foreign Currency (P.L. 480) Program (coordinated for NIH by the Fogarty International Center) in six countries. NIAID was most actively involved in FY 1981 with Argentina, Australia, Brazil, Colombia, the Dominican Republic, Egypt, France, India, Israel, Japan, Kuwait, Mexico, The Netherlands, Nigeria, Pakistan, Panama, the People's Republic of China, Poland, Sierra Leone, Sudan, Sweden, Switzerland, Thailand, the United Kingdom, and Venezuela.

On September 24, 1981, NIAID signed a Participating Agency Service Agreement (PASA) with the U.S. Agency for International Development (USAID) to administer a multiple-year project entitled "The Epidemiology and Control of Arthropod-Borne Diseases in Egypt and Israel." The first-year funding at \$1.5 million will provide for research contracts with the Hebrew University (Jerusalem) and Ain Shams University (Cairo), as well as for the participation of U.S. scientists from other Federal agencies and universities. The initial emphasis will be on the epidemiology and epizootology of three diseases: Rift Valley Fever, malaria, and leishmaniasis.

Bilateral Agreements and Other Country-to-Country Activities

NIAID conducts scientific exchange and collaborative research through a variety of mechanisms which extend from informal direct contact between investigators to formal agreements for cooperation between the Governments of the U.S.A. and other countries. Because of the NIAID research responsibilities in tropical diseases, microbiology, and vaccine development, the Institute has a unique need to foster cooperation with scientists and institutions in developing countries. In recent years, there has been a proliferation of formal bilateral science and technology agreements with developing countries. In addition, there has been a trend for existing and new bilateral programs to move into additional areas such as immunology and genetic engineering.

Argentina

In February 1981, the Minister of Health of Argentina visited NIAID to discuss the prospects for expanded collaboration in Chagas' disease (American trypanosomiasis) and Argentina hemorrhagic fever under the terms of the U.S.-Argentina Science and Technology Agreement. A scientist in the Laboratory of Parasitic Disease presently collaborates with the Instituto "Fátala Chaben" (Buenos Aires) on the cell biology of *Trypanosoma cruzi* strains and single-cell isolate clones.

Australia

During FY 1981, there was an exchange of information between the Governments of Australia and the U.S.A. on recombinant DNA guidelines and policies. NIAID continued its productive extramural collaboration in immunology with scientists at the Walter and Eliza Hall

Institute of Medical Research. Three active grants there supported research on the development of model parasite vaccines, mechanisms of lymphocyte-antigen interactions, and T cell development in the thymus.

Bangladesh

NIAID collaborative research with the International Center for Diarrheal Disease Research/Bangladesh is with the Laboratory of Infectious Diseases in the epidemiology of rotavirus infection.

Brazil

During FY 1981, four of the 10 active ICIDR awards totalling \$1,128,808 went to the U.S. investigators for collaborative studies in Brazil. Cornell University Medical College collaborates with the University of Bahia on Chagas' disease and the endemic forms of cutaneous, mucocutaneous, and visceral leishmaniasis. The Harvard School of Public Health is involved in collaboration with the University of Bahia and the Fundação Oswaldo Cruz (FIOCRUZ), Rio de Janeiro, on Chagas' disease and schistosomiasis. The presence of three full-time U.S. scientists has led to the establishment of a multidisciplinary Brazilian-U.S. team with competence in the fields of epidemiology, clinical medicine, immunology, and entomology. In February 1981, the University of Bahia hosted a 1-day symposium to review the research activities of Brazilian and U.S. scientists associated with the projects.

The University of South Florida is the recipient of an ICIDR exploratory grant to collaborate with scientists at FIOCRUZ on studies of the spread of schistosomiasis in newly developed agricultural colonies in Northeast Brazil (Piauí). A Columbia University investigator is involved in a collaborative study with the Federal University of Rio de Janeiro to use lectins to study the cell surface carbohydrates of virulent and avirulent forms of *Leishmania*.

Intramurally, collaboration continues with the University of Goiás (Goiana) on the HLA tissue-typing of patients with Chagas' disease. More detailed studies of the immune response of selected patients is being planned. FIOCRUZ and Conselho Nacional de Pesquisa (CNPq) scientists are exploring with NIAID collaboration in tropical medicine.

Canada

NIAID supports an investigator-initiated grant award at the University of Manitoba on the suppression of the IgE response.

Colombia

Tulane University's collaborative research with COLCIENCIAS (Colombian Fund for Research) will continue under the ICIDR mechanism with emphasis directed toward both epidemiological and basic biological investigations of selected vector-borne diseases, especially filariasis and trypanosomiasis. As examples of the range of the ICIDR activities, *Dipelatonema perstans* microfilaremia has been documented in 31 percent of the population of the Amazon Basin (Guainia Territory). In the laboratory, an enzyme-linked, immunosorbent (ELISA) test is being used to study levels

of humoral immunity in the serum of patients with filariasis. The Cali Center has also succeeded in attracting complementary grant support from WHO and the Canadian International Development Research Center.

Congo/Brazzaville

At the request of the U.S. Ambassador, NIAID scientist administrators visited Brazzaville in November 1981 to explore possible linkages in tropical medicine between NIAID and the People's Republic of the Congo.

Czechoslovakia

The Laboratory of Immunology collaborates with the University of Prague on immunoglobulin genetics, including the regulation of gene expression and lymphoid differentiation.

Dominican Republic

The Laboratory of Parasitic Diseases continues its collaborative studies of leishmaniasis with the Instituto Dermatologico (Santo Domingo). The Dominican Republic has a uniquely high incidence of diffuse cutaneous leishmaniasis, a rare manifestation previously reported in Ethiopia and Venezuela. It appears that the Dominican leishmanial strain is different from the *L. mexicana* and *L. brasiliensis* prevalent elsewhere in Latin America. Studies on four Dominican patients at the Clinical Center, however, indicate that the major determinant may be an HLA-linked primary macrophage-antigen-handling defect. These patients did not respond to Pentostam but had a good initial response to Amphotericin B. Of interest is that one patient with bilaterally symmetrical lesions responded to local hyperthermia.

Egypt

NIAID has also been involved in collaborative research with Egyptian investigators for more than a decade, most recently under the terms of the U.S.-Egypt Agreement for Collaboration in the Areas of Science and Technology. During FY 1981, NIAID collaboration was primarily through P.L.-480 projects. Because new P.L.-480 awards stopped in FY 1981, NIAID will phase out some of these projects. In other instances, NIAID staff will work with U.S. and Egyptian scientists to obtain alternate sources of funding.

In addition to direct involvement, NIAID is involved in collaborative efforts with CDC-administered P.L.-480 projects. The Laboratory of Infectious Diseases and the NIAID-funded Infectious Enteric Diseases Study Center at the University of Texas (Houston) provide virologic and bacterial support, respectively, to the Diarrheal Diseases Project at the Epidemiology Study Center in Bilbais.

Federal Republic of Germany

The exchange of guidelines and technical information continues with the Federal Ministry for Research and Technology (BMFT). NIAID also provides grant support to the Max Planck Institute for Biology on the polymorphism of the major histocompatibility complex.

Finland

In FY 1981, NIAID extended its contract with the Central Public Health Laboratory to provide followup studies of children immunized with meningococcal type A vaccine from 1974 to 1978. The original contract resulted from a 1973 request from the Finnish National Board of Health for assistance in dealing with an epidemic of that disease. The new contract includes evaluation of the response to *Hemophilus influenza*, type B vaccine administered as a control in the 1974 efficacy trials. NIAID also supports one grant to the University of Helsinki to study the regulation of immune response by specific factors.

France

During FY 1981, NIAID continued the support it has provided for 20 years to 1980 Nobel Laureate Dr. Jean Dausset on skin grafts and surface leukocyte antigens. Intramural scientists collaborate with the Institut Pasteur on genetic studies of immunoglobulins and other serum proteins; with the CNRS on the structure and activity of immunologically important cells and proteins; and with the Faculty of Medicine/Brest on tick-borne disease agents. An INSERM scientist was hosted for 4 months to study the generation of suppressor and cytotoxic T cells directed to paternal antigens in postpartum mice.

Ghana

The Laboratory of Parasitic Diseases increased its scientific exchange and developed plans for a collaborative project on the chemotherapy and immunology of filariasis with investigators at the Tamale Hospital.

Haiti

The Tulane ICIDR Program has developed a collaborative project in Haiti on the epidemiology of filarial infection at the Institut Franais d'Haiti.

Hong Kong

An NIAID science administrator visited the Chinese University of Hong Kong in December 1980 to review the antiviral research project there which screens Chinese traditional herbs. As a result, two NIAID contract recipients evaluated "guan-zhong," which had shown anti-influenza activity *in vitro* in animal models. While both investigators documented modest effects of a partly purified herbal extract, they also demonstrated *in vitro* and *in vivo* toxicity. As the toxic and active agents may be different, NIAID has recommended that further characterization be carried out.

India

NIAID has participated over the years in collaborative research with Indian investigators, funded largely through the P.L.-480 program. In February 1980, the Indian-U.S. Working Group on Health of the Joint Science and Technology Committee met in New Delhi to review and redefine priority diseases for collaborative research. The mutually agreed upon areas for emphasis were: diarrheal diseases; filariasis; hepatitis; leprosy; malaria; recombinant DNA technology;

rheumatic fever and sequelae; and tuberculosis. NIAID reviewed the status of these activities with the Senior Deputy Director, Indian Council for Medical Research (ICMR), during a visit to NIH in June 1981.

In February 1980, the Joint Working Group on Health endorsed the concept of an Indo-U.S. Workshop on Diarrheal Diseases. The Workshop is now scheduled to be held at the ICMR Headquarters in New Delhi from February 17 to 20, 1982. Approximately 10 U.S. and 30 Indian scientists will participate in sessions devoted to promoting scientific exchange and collaboration in epidemiology; ecology; bacterial, viral, and parasitic agents; clinical management; infection-nutrition interaction; immune mechanisms; and the application of recombinant DNA technology to diarrheal disease research.

During FY 1981, collaboration was begun with the Kothari Centre for Gastroenterology (Calcutta) on the axenic culture of *Entamoeba histolytica* and the nutritional iron status of patients with amebiasis.

An NIAID scientist visited the Tuberculosis Research Center (Madras) for 3 weeks in September 1981, in a continuation of a collaborative effort which began in 1975 on the immunology of filarial infections and the pathogenesis of tropical eosinophilia and lymphangitis. This "no-cost" proposal is now moving into two new clinical areas: the long-term effect of diethylcarbamazine (DEC), mebendazole, and DEC-mebendazole on lymphatic pathology and the development of elephantiasis; and the natural history of asymptomatic microfilaremia with and without chemotherapy.

Another NIAID scientist continues his collaborative studies at the National Institute of Virology (Poona) on the epidemiology of hepatitis in India. With the application of recently developed laboratory tests, it is now apparent that the massive water-associated outbreak of hepatitis in Delhi in 1955-56 was neither hepatitis A nor B. Ongoing studies indicate that non-A, non-B hepatitis is a common source of epidemic and sporadic hepatitis in India. NIAID has been able to produce hepatitis in chimpanzees following the inoculation of infectious Indian material, but has not yet recovered an etiologic agent. Efforts are now under way to develop a study with the National Institute of Virology on the epidemiology of hepatitis of pregnancy and childhood cirrhosis.

During FY 1981, the Government of India made a policy commitment to eliminate leprosy as a public health problem by the end of the century. Indo-U.S. collaboration in leprosy has been shared within the PHS among the National Center for Hansen's Disease in Carville, Louisiana, NIAID, and CDC.

An ICIDR exploratory grant has been awarded to the University of Hawaii to collaborate with the Aligarh Muslim University on the *in vitro* cultivation of human malarial parasites isolated in India, the drug susceptibility of *Plasmodium falciparum*, and the culture of Indian *P. vivax* strains *in vitro*. An NIAID scientist visited the Central Drug Research Institute (Lucknow) in September 1981 to complete the preparation of two collaborative protocols, entitled: "The identification of immunogens and immunosuppressive molecules in pri-

mate malarias" and "Studies on immunity to the sexual stages of the malarial parasite."

During FY 1981, plans for a fixed-site Indo-U.S. Workshop on Recombinant DNA were modified in favor of the visit of a team of four U.S. scientists led by the current Deputy Director of NIAID in March 1982. The team will become familiar with the leading Indian scientists and institutions active in this area and develop recommendations for immediate scientific exchange and opportunities for longer-term NIAID-, NHLBI-, and FIC-cosponsored and -provided funds for a Conference-Workshop on Rheumatic Fever in the 1980's (New Delhi: March 2-5, 1981). Although developed within the Indo-U.S. Joint Health Program, scientists from Asia, the Western Pacific, the Near East, Europe, and Latin America participated. The American Heart Association coordinated the U.S. effort. Publication of the proceedings is expected in FY 1982. While it is too early to evaluate the extent to which the Conference served as a catalyst for collaborative research, efforts are under way between the University of Tennessee and the ICMR Streptococcal Typing Center (New Delhi) to study the epidemiology of group M streptococcal protein in India.

Israel

Two intramural laboratories collaborate with the Hadassah Medical Center (Jerusalem). The Laboratory of Streptococcal Disease is involved in studies which relate the electron microscopic appearance of bacteria to their structure and function. The Laboratory of Microbial Immunology is active in the characterization of surface IgG in the clones of a murine B cell lymphoma. The three NIAID extramural grants to Israeli investigators are concerned with: the bioenergetics and control of bacterial behavior; the exploration of new approaches to marrow and organ transplantation; and the differentiation and activity of mast cells in culture.

Italy

During FY 1981, NIAID supported three extramural projects within the Italy-U.S. bilateral Understanding on Cooperation in the Field of Health and Medicine. These awards to U.S. scientists at Roswell Park Memorial Institute, Temple University, and Rockefeller University are in the areas of biosynthesis of bacterial cell walls and membranes, immunological studies with cultured human lymphocytes, and studies of myeloma protein and antibodies.

Japan

NIAID is currently involved in two Japan-United States initiatives. The first is the U.S.-Japan Cooperative Medical Science Program (JCMSP), initiated in January 1965. Under the terms of this agreement, both countries have undertaken joint cooperative biomedical research in diseases of particular importance in Asia. Under Public Law 86-610 (the International Health Research Act of 1960), the State Department coordinates foreign relations and policy while DHHS is responsible for the scientific elements of the program. NIAID has been the lead Institute within NIH and DHHS since 1968.

Although the JCMSP operates as a bilateral program, scientists from other countries and/or international agencies often participate. Applications submitted within the context of this program by U.S. scientists compete for available funds on the basis of scientific merit without a special NIAID budget set-aside. Japanese scientists, on the other hand, depend upon the Program to facilitate their funding proposals.

At the present, the JCMSP consists of panels on: leprosy, tuberculosis, cholera, hepatitis, parasitic diseases (schistosomiasis and filariasis), viral diseases (arboviruses, rabies, rotaviruses), environmental mutagenesis and carcinogenesis, and malnutrition. These panels meet annually either in the U.S.A. or Japan. The Director of NIAID and staff members serve as the Secretariat to the U.S. Delegation to the JCMSP and to six of the panels. The Third Five-year Report (1975-1980) of the JCMSP became available in September 1980.

JCMSP Panel Meetings during FY 1981 included the following: Hepatitis (Hakone: November 20-21, 1980); Leprosy (Bethesda: July 13-14, 1981); and Tuberculosis (Bethesda: July 13-15, 1981). The U.S.-Japan Immunology Symposium (Tokyo: October 13-15, 1980) focused on four areas: the regulation of immune response by MHC and idiotype; molecular biology of B lymphocyte differentiation; hybridomas and functional cell cloning; and differentiation and functions of human lymphocyte subsets.

Following the October 1980 Immunology Symposium, the joint committee approved in principle the inclusion of immunology within the JCMSP, but referred the matter to the Subcommittee on Program Review and Planning for further deliberation. In February 1981, the subcommittee met in Honolulu and recommended that the new area be known as the Immunology Board to reflect both its disciplinary, rather than disease, orientation and the involvement of the Ministry of Education. At its July 16-17, 1981 meeting in Bethesda, the joint committee explored the problem of how to reduce spending, especially travel, without sacrificing the mission of the program. The joint committee made the policy recommendation that unilateral changes were not in order due to the different funding mechanisms in the two countries. Mechanisms for effecting changes and cost reductions will be discussed at the next subcommittee meeting (Honolulu: February 11-12, 1982).

On May 1, 1980, the President of the United States and the Prime Minister of Japan signed the Japan-U.S. Science and Technology agreement for Non-Energy Cooperation, which will be separate from, but coordinated with, the JCMSP. Within this second bilateral program, NIAID has lead responsibility for three program areas: immunization (vaccine development), recombinant DNA research, and antiviral agents.

Since then, guidelines for recombinant DNA research have been exchanged, and the Japanese Coordinator has participated in the meetings of the U.S. Recombinant DNA Committee. In November 1980, NIAID/NIH hosted an informal group of Japanese interferon researchers touring the U.S. The First

Meeting of the U.S.-Japan Cooperative Program for Recombinant DNA Research (Honolulu: February 2-5, 1981) continued the exchange of scientific information on host-vector systems and risk assessment. The participants also developed a Memorandum of Understanding, subsequently signed by the U.S. and Japanese coordinators, which provided the basis for activities in FY 1981-82.

At the first Meeting of the U.S.-Japan Program for Cooperation in Science and Technology (Tokyo: September 24-25), both countries agreed to continue to develop recombinant DNA research activities within the Science and Technology Program. The technical aspects of vaccine development and antiviral agents, however, will remain with the appropriate JCMSP panel. Matters requiring policy review and decisions will be referred to the U.S. Chairman of the Science and Technology Program.

Outside the two formal bilateral programs, three intramural laboratories have ongoing collaboration with Japanese scientists. One is actively involved with the University of Tokyo in the fractionation of lymphoid cell subsets with lectins that specifically bind to cell surface glycan differentiation markers. The Rocky Mountain facilities also maintain collaboration with scientists at the National Institutes of Health in Tokyo on tick-borne disease agents and the characterization of human papovaviruses.

Kuwait

An NIAID scientist traveled to Kuwait from April 3 to 10, 1981, as a consultant to the Ministry of Public Health in the development of a national allergic disease program and the feasibility of an Allergy Research Center.

Mexico

The University of Washington has an exploratory ICIDR award to work with the Instituto Nacional Politecnico (Mexico City) on the serodiagnosis of subclinical leprosy. The Laboratory of Parasitic Diseases continues collaborative research with Mexican scientists and the Center for the Study of Amebiasis (Mexico City) which began over 10 years ago.

Netherlands

Three intramural laboratories have ongoing collaborative research activities with counterparts in The Netherlands: the State University of Utrecht is involved in studying the specificity of immune responses; The Netherlands' Red Cross Book Transfusion Service is studying the mechanisms of immune recognition of viral antigens; and the Catholic University of The Netherlands is studying the taxonomy, ecology, and colonization of parasitic arthropods of medical importance. Two research contracts with the University of Leiden are concerned with the acquisition of homozygous typing cells and antisera to HLA-A, -B, and -C loci and B cells.

Nigeria

Ohio State University has an active ICIDR exploratory

grant with the University of Nsukka to study the biological control of mosquitoes which transmit malaria by *Bacillus thuringiensis*. A Nigerian Visiting Fellow is carrying out investigations on the binding of red blood cells infected with malaria to the endothelium of blood vessels. NIAID staff have also participated actively in the development of the biomedical research component of the U.S.-Nigeria Joint Task Force on Health Cooperation (Bethesda: February 9-12, 1981).

Pakistan

While the University of Maryland International Center for Medical Research (ICMR) at the Pakistan Medical Research Center (Lahore) terminated in May 1980, NIAID continues to support an investigator-initiated project on the ecology of mosquitoes in Pakistan and the genetic control of *Anopheles culicifacies*, an important vector of malaria in that country.

Panama

During FY 1981, NIAID supported the Gorgas Memorial Laboratory through the Gorgas Memorial Institute (Washington, D.C.) for investigations in Panama on the transmission and reservoirs of the St. Louis virus in tropical ecosystems. The Gorgas Institute also collaborates with the NIAID-supported Yale Arbovirus Research Unit (YARU) on the epidemiology of the yellow fever virus.

People's Republic of China

The U.S.-PRC Joint Committee on Science and Technology in Medicine and Public Health held its first meeting in Beijing in June 1979. At that time, NIAID was assigned lead responsibility for immunology, and secondary responsibility with the Centers for Disease Control (CDC) in parasitology and infectious diseases. The parasitic and infectious diseases emphasized in the bilateral health protocol are: malaria, schistosomiasis, hepatitis, and influenza. NIAID subsequently assumed the lead role in recombinant DNA research.

As a result of the exchange visits of the U.S. and Chinese coordinators in FY 1980, the protocol for cooperation in immunology was modified for FY 1981-82 to include the immunology of infectious and parasitic diseases; cancer; diseases of the immune system, including primary immune deficiency diseases; and autoimmunity and allergy and skin and organ transplantation. The research approaches will involve immunobiology, immunogenetics, molecular immunology, immunopharmacology, and clinical immunology. The Immunology Work Plan provides for scientific exchange, research training, working groups, and collaborative research in immunogenetics and clinical immunology. The U.S.-PRC Joint Committee endorsed these modifications at its second meeting (Tianjin: November 20-21, 1980).

During May 1981, NIAID hosted the 3-week visit of three Chinese allergists who toured clinical and research facilities in Washington, Baltimore, New York, Boston, and La Jolla.

NIAID signed an interagency agreement (\$37,000 in FY 1981) with CDC in September 1981, to share costs on the collaborative protocol with the Institute of

Virology (Beijing) and Shanghai First Medical College to study the efficacy of the NIH inactivated hepatitis B vaccine in the prevention of transmission of infection from hepatitis B antigen (HBsAg) carrier mothers. Comparison of the antigenicity of the U.S.-produced vaccine in Chinese adult volunteers is under way. NIAID also sponsored the 3-month visit of the Deputy Director of the Department of Hepatitis and Influenza, National Serum and Vaccine Institute (Beijing), to NIAID and the Bureau of Biologics to become familiar with hepatitis vaccine production and quality control techniques.

Poland

During FY 1981, NIAID involvement in the Polish-U.S. Agreement on Cooperation in the Field of Health consisted of two P.L.-480 projects with extramural scientists on the immunochemistry of *Shigella* lipopolysaccharides and the role of macrophage surfaces in the regulation of immune response.

Sierra Leone

NIAID and FIC continued to share the costs of an interagency agreement with CDC for studies on *Mastomys natalensis* (a multimammate mouse) and Lassa fever in rural Sierra Leone. The project attempts to characterize the populations of *M. natalensis*; determine the relationship of genetic subpopulations of mice to transmission of Lassa fever to humans; describe the epidemiologic and socioeconomic factors associated with transmission in the village and develop techniques to prevent rodent-human transmission.

South Africa

NIAID currently supports a research contract with the State University of New York (Syracuse) which will provide for collaboration with the Bureau of Biologics (FDA), the South African Institute for Medical Research (Johannesburg), and the University of Cape Town to test the efficacy of the new Bureau of Biologics' meningococcus, type B polysaccharide vaccine in infants and young children during the ongoing epidemic of that disease in South Africa. Safety and efficacy studies had previously been carried out in U.S. children at NIAID Vaccine Evaluation Centers in Baylor and the University of Vermont.

Spain

An NIAID scientist was a member of the four-person U.S. team sent during the summer of 1981 to assist the Spanish Government with the investigation, management, and control of the toxic oil poisoning associated with an adulterated batch of commercial olive oil.

Sudan

Michigan State University has an ICIDR program project award to collaborate with the Ministry of Health on the clinical trials of new antischistosomal drugs (e.g., oltipraz), the *in vitro* cultivation and drug-sensitivity testing of malarial strains from the Sudan, the ecology of *Simulium damnosum*, and the epidemiology of human orchocerciasis. Collaborative arrangements have been made with the WHO Malaria Training Center (Sennar),

USAID, Rhône Poulenc (Paris), and West German investigators.

Sweden

During FY 1981, NIAID initiated discussions with Swedish health authorities on bilateral epidemiological research opportunities in the Stockholm County Health Care Information System. At the present time, NIAID and Swedish intramural scientists are collaborating in two areas: with the Universities of Lund and Uppsala on the molecular aspects of mycoplasma-eukaryocyte interactions and with the University of Uppsala on the structural and functional relationships of bacterial antigens in the immune response.

Switzerland

NIAID intramural scientists have active collaboration with Swiss investigators at Basle on the immunology and chemotherapy of systemic mycoses and at Neuchatel on the natural history and public health significance of a previously unrecognized rickettsia in the *Ixodes ricinus* tick similar to the Rocky Mountain Spotted Fever agent. An investigator-initiated grant to the University of Zurich supports studies on the *in vitro* and *in vivo* specificity of virus immune t cells.

Thailand

The University of Illinois has an ICIDR program project award which involves collaboration with the Universities of Cincinnati, New Mexico, and Chiang Mai and the McKean Rehabilitation Institute in four interrelated areas: the epidemiology and seroepidemiology of leprosy infection and disease; HLA genetic studies of susceptibility to leprosy; the immunoregulatory abnormalities and immunopathology of leprosy; and phagocytic cell functions and metabolism in leprosy.

U.S.S.R.

NIAID's formal involvement in the U.S.-U.S.S.R. Agreement for Cooperation in the Fields of Medical Science and Public Health has been limited to influenza. This initiative, under the coordination of CDC, provides for exchange of information, scientific meetings, visits by scientists, and a mutual exchange of virus strains and laboratory reagents.

United Kingdom

The Medical Research Council Clinical Research Centre (Harrow) collaborates on the electron microscopy of bacteria and on mycoplasma. The London School of Tropical Medicine and Hygiene is active in studying the biochemical and genetic mechanisms of obligate intracellular parasites, in the role of bacterial antigens in immune response, and on immune responses to rickettsial infections and the Legionnaire's bacterium. Two extramural research grants to the University of London deal with the regulation of immune responses by specific factors and the immunogenetic regulation of t cell-macrophage interaction. Four English scientists hold NIAID research training grants in diverse areas, including the role of complex oligosaccharides in nematode development.

Venezuela

NIAID laboratories are collaborating with the University of Caracas in epidemiological, clinical, and biochemical studies of human enteroviral infection. As nine of the 10 priority areas in the biomedical and epidemiological research component of the draft U.S.-Venezuelan Joint Health Agreement are communicable diseases, Dr. Krause is serving as the interim coordinator. In July 1981, Drs. Krause and Western visited the Pan American Center for Research and Training in Tropical Diseases (CEPIALET), the Venezuelan Institute for Scientific Investigation (IVIC), the Tropical Medicine Institute (IMT), the Torrealba Institute, the National Institute of Health (INH), and "La Trinidad" Medical Teaching Center to determine the present level of scientific exchange and opportunities for new and expanded collaboration.

Zambia

NIAID has long-standing scientific exchange with the Tick Diseases Unit (Lusaka) in the morphology and classification of African specimens. In May 1981, the WHO team leader of the Tropical Disease Research Center (Zambia) visited NIAID.

Zimbabwe

Following a visit to NIAID by the Secretary of the Ministry of Health in September 1980, NIAID has begun the exchange of scientific information with the Blair Research Institute. An NIAID Staff Fellow spent 3 months in the Infectious Diseases Service of the University Hospital (Salisbury).

Multilateral Activities

At present, NIAID intramural laboratories serve as WHO Collaborating Centers in rickettsial diseases, mycoplasma, and respiratory viruses other than influenza. During FY 1979, WHO designated the NIAID Microbiology and Infectious Diseases Program as one of three collaborating centers on interferon. The NIAID extramural program also provides indirect support to U.S. institutions that serve as WHO Collaborating Centers. Among the most active are WHO Collaborating Centers in arboviruses (Yale), enteroviruses (Baylor), influenza (CDC and St. Jude Children's Research Hospital), and immunology (Scripps Clinic). At the invitation of WHO and TDR, NIAID staff and awardees participated actively in meetings or expert panels, as consultants to WHO or member countries, or as faculty in WHO-sponsored training activities. NIAID staff are particularly active in support of the WHO Immunology Program, including participation in the annual WHO Immunology Course in Lausanne.

Extramural Programs

The NIAID extramural portfolio in Tropical Medicine is drawn from nine areas of the Microbiology and Infectious Disease Program (MIDP). These are: tropical diseases; the ICIDR and TRU Programs; general parasitology; tropical virology; tropical bacteriology; tropical mycology; rickettsiae; and vector pathogens.

In May 1980, NIAID phased out the *International*

Centers for Medical Research (ICMR) program which had been in operation since 1960. The ICMR program had originally been established in the NIH Office of International Research under the authority of Public Law 86-610 (International Health Research Act of 1960) and was transferred to NIAID in 1968. An ICMR was a discrete research organization sponsored by a U.S. health institution to provide a stable base for research and training through research centers located overseas. Collectively, the four ICMR units in Kuala Lumpur (Malaysia), Dacca (Bangladesh), Lahore (Pakistan), and Cali (Colombia) served as a national resource to provide a pool of investigators in tropical diseases and to stimulate young scientists to pursue careers in international biomedical research.

NIAID has superseded the ICMR Program with four award mechanisms which are intended to provide greater flexibility and cooperation between U.S. tropical medicine specialists and scientists in developing countries. They are: the International Collaboration in

Infectious Disease Research (ICIDR) Program; the Tropical Disease Research Units (TRU); the International Tropical Disease Research (ITDR) Fellowships; and the Senior International Fellowships with an emphasis in tropical diseases.

The ICIDR program differs from the ICMR in several respects. Perhaps the most important is the emphasis given to developing a peer relationship between the U.S. institution or investigators and their counterparts. The program focus will be on infectious diseases, and at least 70 percent of the award must be spent overseas. The ICIDR program has two parts. Program project (part A) grants are for collaborative research in a series of related projects. Exploratory project (part B) grants are between individual scientists in a single area. The current part A and B awards totaling \$2.6 million by principal U.S. investigators, cooperating institutions, and major research emphasis are shown below.

NIAID International Collaboration in Infectious Disease Research (ICIDR) Program FY 1981

Part A. Program Project Grants

U.S. University/Principal Invest.	Foreign Institution/Country	Research Interest	Estimated Budget
Harvard School of Public Health (Dr. T.H. Weller)	Federal University of Bahia, <i>Brazil</i>	Schistosomiasis Chagas' Disease	\$ 295,203
University of Illinois (Dr. K.C. Nelson)	Chiang Mai University, <i>Thailand</i>	Immunobiology and Epidemiology of Leprosy	385,634
Cornell University Medical College (Dr. T.C. Jones)	Federal University of Bahia, Brazil and University of Brasilia, <i>Brazil</i>	Leishmaniasis Trypanosomiasis	709,601
Michigan State University (Dr. J.F. Williams)	Central Laboratory, Ministry of Health, Khartoum, <i>Sudan</i>	Schistosomiasis Orchocerciasis Malaria	429,266
Tulane School of Public Health (Dr. T.C. Orihel)	Colciencias Cali, <i>Colombia</i> and Institut Français d'Haiti Port-au-Prince, <i>Haiti</i>	Filariasis Trypanosomiasis Leishmaniasis Intestinal Parasites	487,836
Subtotal Part A			2,307,540

Part B. Exploratory Development Grants

University of Washington (Dr. T.M. Buchanan)	National School of Biological Sciences, National Polytechnic Inst., Mexico City, <i>Mexico</i>	Leprosy	42,038
University of South Florida (Dr. G.E. Rodrick)	Fundação Oswaldo Cruz, Rio de Janeiro, <i>Brazil</i>	Schistosomiasis	25,838
University of Hawaii (Dr. W.A. Siddiqui)	Aligarh Muslim University of Aligarh, <i>India</i>	Malaria	59,619
Columbia University (Dr. P. D'Allessandro)	Federal University of Rio de Janeiro, <i>Brazil</i>	Visceral Leishmaniasis	98,166
Ohio State University (Dr. J.D. Briggs)	University of Nigeria, Nsukka, <i>Nigeria</i>	Vectors of Human Disease/Malaria	51,367
Subtotal Part B			\$ 277,028
Total ICIDR			\$2,584,568

NIAID Tropical Disease Research Unit (TRU) Program: FY 1981

Robert Breck Brigham Hospital (Dr. J. David)	Immunology of Chagas' Disease, Filariasis, and Leishmaniasis	466,894
Case Western Reserve University (Dr. A. Mahmoud)	Multidisciplinary in Parasitic Infections (Schistosomiasis)	248,640
Total TRU		\$ 715,534

The Laboratory of Parasitic Diseases and the Rocky Mountain facilities have functioned for many years as Federal laboratories committed to basic research in tropical diseases. The Yale Arboviral Research Unit (YARU) has, with NIAID support, provided a University-based center of excellence in tropical virology. The NIAID-funded TRU program is designed to expand this network through awards to outstanding U.S. institutions for multidisciplinary research in tropical medicine. In addition to new knowledge, this program will provide the opportunity for institutional strengthening, research training for young U.S. and foreign scientists, career development, and a domestic counterbalance to the ICIDR initiative overseas. During FY 1981, the TRU award to the Robert Breck Brigham Hospital, Harvard University, continued, and ongoing support to Case Western Reserve was incorporated into the TRU program.

The ITDR Fellowship program was initiated in 1979 with NIAID funds to provide a limited number of postdoctoral fellowships for advanced training in tropical disease research in the U.S.A. for scientists from developing countries. As applications were encouraged from countries without FIC/NIH nominating committees, the WHO regional and country offices and the TDR Programme have cooperated in screening candidates. In FY 1981, an Indian and Peruvian scientist completed the first two ITDR awards for research training in leprosy and malaria, respectively. No new awards were made during the fiscal year.

The Senior International Fellowship (SIF), with an emphasis in tropical diseases, is a special competition for mid-career and senior U.S. scientists to spend 3-12 months in cooperative research projects on tropical medicine outside the U.S.A. The initial three awards for overseas research in Kenya, The Netherlands, and the U.K. were carried out during FY 1981. The Fogarty International Center administers both the ITDR and the SIF/Tropical Diseases Fellowships.

Advances in immunology have increased the international activities of the Immunology, Allergic and Immunologic Diseases Program (IAIDP). IAIDP, for example, supports the work of the International Bone Marrow Transplantation Registry maintained at the Mt. Sinai Medical Center in Milwaukee and the Hybridoma Bank at the American Tissue Culture Collection (ATCC) in Rockville, Maryland. IAIDP staff are active in the International Union of Immunological Societies (IUIS)-WHO Committees on Standardization. In addition to WHO consultant services, IAIDP participated in bilater-

al immunology initiatives with Japan, Kuwait, and the People's Republic of China.

Competing Foreign Awards

Non-U.S. scientists may compete for NIAID grant awards and apply directly for "sole-source" contracts in any program area. In FY 1981, foreign awards totaled \$1,146,459 and constituted 3.7 percent of the tropical medicine international research budget. Of the 27 awards to investigators in 11 countries, however, only one research and three training grants (\$58,355) were relevant to tropical medicine. No principal investigator came from a developing country. The 27 FY 1981 foreign awards represent a significant decline from the 46 awards (\$1,215,238) in FY 1980. This is due primarily to 14 fewer training grants to English scientists. Since FY 1979, competing foreign awards have declined nearly 10 percent in fixed dollars.

Reagents and Reference Material

While the major functions of the NIAID Extramural Activities Program are program analysis, project review, and grant or contract management, its Research Resources Branch (RRB) also coordinates the Institute's substantial activities in providing reagents and resources without charge to investigators and government agencies throughout the world. During FY 1981, NIAID maintained 18 major grants or contracts for the distribution of micro-organisms, parasites, or animals for research which were relevant to tropical medicine. Additional reference materials are frequently provided on a less formal basis by intramural laboratories.

During this period, NIAID also completed a research contract with the University of Alabama to determine optimal conditions for the preservation, retrieval, storage, and distribution of fragile bacterial host strains. The study has resulted in specifications for "Packaging, Maintaining and Distributing Bacterial Host Strains and Bacteriophage Vectors for Recombinant DNA Research." The RRB also arranged for the processing and packaging of additional hypersensitivity antigens and antisera such as short ragweed extract and an antibody to this extract, which will be offered to WHO as a reference preparation. New procurement contracts will also provide several other new reagents, including rotavirus type 2, hypersensitivity pneumonitis, and penicillin minor determinant mixture.

RRB continues to distribute a variety of allergenic products for *in vitro* or investigational use which include

venoms of honey bees, yellow jackets, and hymenoptera venom diluent. Limited contract funds, however, are forcing a consolidation or reduction of some services. American Type Culture Collection (ATCC), for example, is now totally responsible for the distribution of the NIAID enterovirus, adenovirus, rhinovirus, and arbovirus reagent collections. While NIH scientists continue to receive these research reagents at no cost, all other U.S. and foreign investigators are required to pay a nominal ATCC handling fee and shipment costs.

The NIAID intramural program now comprises 12 research laboratories, three of which are located at the Rocky Mountain facilities in Hamilton, Montana. Although all have significant international health activities, the major portion of tropical medicine research is concentrated in the Laboratory of Parasitic Diseases (LPD). The Epidemiology Branch (EB) of the Rocky Mountain Laboratory facilities also devotes a substantial portion of its resources to medical zoology and vector studies. The Laboratory of Infectious Diseases (LID) is becoming increasingly involved in collaborative investigations on respiratory viruses, diarrheal diseases, and hepatitis. The apparent increase in intramural research to \$6.5 million in FY 1981 from \$3.6 million in last year's NIH International Report is due to a change in assigning costs to individual intramural research projects. The actual level of intramural research remained about the same.

Recent advances in immunology and laboratory techniques are now being applied to diseases prevalent in the tropics with a consequent tendency for broader involvement by basic biomedical research laboratories in international research. The Laboratory of Microbial Immunology (LMI), for example, is active in studying the immune reaction to several parasitic infections such as trypanosomes, malaria, and amebae in experimental models. The Laboratory of Clinical Investigation (LCI) and the facilities at the Clinical Center are available for detailed studies on U.S. or foreign patients with known or suspected tropical diseases.

NIAID intramural investigators collaborate with colleagues outside the U.S.A. in many research areas beyond the scope of tropical medicine in the exchange of data and diagnostic material or the introduction and standardization of laboratory techniques. Collaboration immediately relevant to tropical medicine also occurs within NIH and with other Federal agencies, particularly the Centers for Disease Control (CDC), the Office of Naval Research (ONR), the Walter Reed Army Institute of Research (WRAIR), and the Bureau of Biologics (BOB).

In FY 1981, 27 intramural projects had major input from scientists in 18 foreign countries. England (6) was the most frequent collaborating country named, followed by Egypt (4), India (4), France (3), Japan (3), The Netherlands (3), and Sweden (3). The Dominican Republic, Israel, and Switzerland had two cooperating units. Argentina, Brazil, Czechoslovakia, Germany, Italy, the People's Republic of China, South Africa, and Venezuela each had one. Intramural scientists are also involved in the technical work of bilateral (USAID), multilateral (WHO, PAHO), or voluntary (Rockefeller Foundation, National Academy of Sciences) agencies concerned with tropical medicine and international research. The NIAID intramural program benefits considerably by the participation of foreign scientists who visit through a variety of mechanisms for periods of days to several years. In FY 1981, for example, NIAID provided funds for long-term visiting scientists from countries under the regular NIH Visiting Program.

Conferences, Seminars and Meetings

During FY 1981, NIAID made commitments to fund 22 conferences and workshops, the majority of which included the participation of foreign scientists. The actual level of funding for conferences, however, was about half of what it had been during the previous 3 fiscal years. NIAID staff also participated in a variety of important scientific meetings. A number were of particular international interest:

●October 9-12, 1980:	VIII International Spores Conference	MBL
●October 27-31, 1980:	VIII International Immunopathology Symposium	San Diego
●November 4-7, 1980:	American Society of Tropical Medicine and Hygiene	Atlanta
●November 20-21, 1980:	International Workshop on Mechanisms of Local Immunity	Bethesda
●December 1-6, 1980:	International Conference on the Impact of Viral Diseases on Developing African Countries	Nairobi (Kenya)
●December 17-19, 1980:	International Workshop on Hepatitis A Infections	Athens (Greece)
●January 5-9, 1981:	Meeting on Molecular Biology, Pathogenicity, and Epidemiology of Bacterial Parasites	Santo Domingo (Dominican Republic)
●January 14-16, 1981:	Malaria Immunity and Vaccine Development Workshop	Bethesda
●January 1981:	Workshop on Potential of Human Immune Globulin for the Prevention and Treatment of Bacterial Disease	Bethesda
●February 2, 1981:	Concept Review of Herpes Vaccine	Bethesda
●March 3-4, 1981:	Consensus Development Conference on Reye's Syndrome	Bethesda
●March 8-9, 1981:	Symposium on Current Topics in Biostatistics and Epidemiology	Bethesda
●March 9-13, 1981:	Workshop on Genetic Variation among Influenza Viruses	Salt Lake City

●March 30- April 2, 1981:	International Symposium on Viral Hepatitis	New York City
●May 11-13, 1981:	Planning Workshop on Genitourinary Infections and Outcome of Pregnancy	Bethesda
●May 12-13, 1981:	Workshop on Anti-Viral Therapy of Genital Herpes	Bethesda
●June 7-12, 1981:	XIV International Leucocyte Culture Conference	Heidelberg (Germany)
●June 17-19, 1981:	Immunoparasitology Symposium	Corvallis
●June 18-19, 1981:	Serodiagnosis of Systemic Mycoses	Bethesda
●July 27-31, 1981:	Conference on Bacterial Virulence and Pathogenesis	Hamilton (Montana)
●August 3-7, 1981:	Gordon Conference on Parasitology	
●August 2-7, 1981:	V International Congress on Virology	Strasbourg (France)
●August 22-29, 1981:	International Epidemiological Association	Edinburgh (Scotland)
●September 17-19, 1981:	Workshop on Infectious Diseases in the Aging	Bethesda

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

Introduction

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) is responsible for the conduct and support of biomedical research relevant to a wide range of chronic, disabling disorders. A number of Institute-funded research activities draw upon the talents and investigative expertise of the international scientific community. This report highlights the nature and scope of collaborative and individual international research efforts and activities carried out with NIADDK support as integral parts of the Institute's overall mission.

Continued collaboration with international scientists and funding of projects that may have worldwide impact are ongoing priorities within the NIADDK. It is only through these mechanisms that we can hope to control, prevent, and ultimately eliminate the many chronic and disabling disorders that fall within the purview of the Institute.

Summary of NIADDK International Programs and Activities: Bilateral Agreements

The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases participates in three formal collaborative research programs under the auspices of the Bilateral Cooperative Agreement Program: The U.S.-Japan Malnutrition Panel Research Support Program, which is part of the U.S.-Japan Cooperative Medical Science Program administered by the National Institute of Allergy and Infectious Diseases; the U.S.-U.S.S.R. Cooperative Program in Arthritis, which had its origin in the U.S.-U.S.S.R. Health Exchange Program of 1972, designed to improve collaboration between the two countries in the field of public health and medical science; and the NIH-INSERM Agreement between the NIH and the National Institute of Health and Medical Research of France.

The following sections outline current activities and the progress that has been achieved in these cooperative efforts.

France

Under the agreement program between the NIH and

the National Institute of Health and Medical Research of France (INSERM), substantial scientific collaboration has occurred between the Clinical Endocrinology Branch of the NIADDK and the Unité de Recherche sur la Glande Thyroïde et la Régulation Hormonale of INSERM. The exchange of scientists from both groups has provided excellent opportunities for collaborative research and an effective exchange of personnel in the study of thyroid hormone synthesis and metabolism.

The exchange has been useful and profitable because the investigators from each country normally work on different but related aspects of thyroid physiology and biochemistry. By combining the programs available to each group, new procedures have evolved to resolve specific problems in thyroid function. In addition, many papers have been published jointly by NIH and the INSERM intramural scientists.

A Clinical Endocrinology Branch scientist visited France in fiscal year 1981 to present lectures and collaborate with staff of the Unité de Recherche sur la Glande Thyroïde et la Régulation Hormonale. A scientist of that institute visited NIH in September, and arrangements were made for her return to NIH for a year to conduct research and collaborate with NIADDK intramural scientists.

Israel

A cooperative study between investigators in the Bone Diseases Program, NIADDK, and members of the staff of Hadassah University Hospital in Jerusalem, Israel, involving approximately 300 ambulatory middle-age patients with osteoporosis, is observing the effects of prolonged administration of a combination of calcium, phosphate, and fluoride salts on bone structure and density. The relationship between long-term levels of intake of various dietary components and the prevalence and severity of osteoporosis among patients with different ethnic backgrounds, geographic origins, and dietary customs provided an optimal opportunity for this type of study. New techniques of early diagnosis of osteoporosis through bone densitometry sophisticated enough to discern minimal changes in bone density, particularly in the spinal vertebrae, have been developed.

Japan

U.S.-Japan Cooperative Medical Sciences Program - Malnutrition Panel: The Malnutrition Panel was established as a part of the U.S.-Japan Cooperative Medical Sciences Program in 1966, and is administered by the Digestive Diseases and Nutrition Program of the NIADDK. The panel is concerned with developing solutions to nutritional problems of importance to Asian people through basic, applied, and clinical research. Such research has been supported by the NIADDK, and by the National Institute of Child Health and Human Development (NICHD). These studies may be conducted overseas, or in the U.S., as long as the subject of the research is pertinent to the international problems addressed.

While food availability is no longer a major problem in most countries in Southeast Asia, a number of social, political, and economic forces account for serious inequities in food distribution, and malnutrition continues to be one of the most serious problems in Asian countries, excluding Japan. The most commonly encountered forms of undernutrition are protein-energy malnutrition, iron deficiency, and vitamin A deficiency. Superimposed are various disease states (particularly diarrheal infections) which cause impaired utilization and loss of nutrients. Malnutrition complicated by diarrheal infection is actually the primary cause of death in children under 5 years. Undernutrition has a severe, adverse effect on the outcome of pregnancy, leading to more premature and low birth-weight infants with increased disabilities and inadequate nutrient reserves. Iron deficiency, which is widespread, may interfere with immune responses, cause lowered resistance to infection, and reduce functional physical capacities. Vitamin A deficiency in turn causes many thousands of cases of damaged vision and total blindness in young children each year, especially in Indonesia.

The Malnutrition Panel has identified as program objectives five areas where research effort may most benefit the undernourished of Asia. These are:

- Influence of environmental and host factors on nutritional requirements.
- Health significance and methods of preventing iron deficiency.
- Interaction of nutrition, immune competence, and infection.
- Effects of nutrition on physical and mental development, behavior, physical capability, and work performance.
- Health consequences of different (and changing) dietary patterns and food habits.

During fiscal year 1981, 16 research grants were active which dealt with the objectives of the U.S.-Japan Malnutrition Panel. Funds provided amounted to \$1.1 million, almost equally divided between NIADDK and NICHD.

Studies have been conducted at the University of Colorado involving dietary zinc supplementation in 3-to 6-year-old children at or below the 10th percentile for body weight and height. It was observed that male children given 10 mg of oral zinc per day gained in height significantly more than did controls. This effect

was not observed in female children. A marked improvement in appetite was also observed in those given the zinc supplement. These observations suggest that zinc supplementation may improve appetite and growth velocity in populations where marginal zinc deficiency exists.

Studies by scientists at the Louisiana State University, supported by NICHD, show that pregnant primates can withstand diets containing as little as 3.35 percent protein (casein) without obvious ill effects to themselves. This level is well below that consumed by most primate populations. Moreover, the offspring were normal when tested by numerous physiological, behavioral, and growth measures, provided the babies were well-fed after birth. Louisiana State scientists concluded that most primates, probably including humans, may be well-adapted to withstand temporary lower protein intakes during pregnancy.

In studies with malnourished children (ages 6-16 years) supported by NICHD and conducted in Cali, Colombia, it was found that the total maximum oxygen consumption and carrying capacity was depressed as compared with normal controls. These and other similar studies suggest that adult work capacity for a given malnourished individual (or one whose physical development was limited due to chronic malnutrition throughout childhood) may be less than that of average American or Western individuals.

Continuing studies on the nutritional suitability of common staple foods for child-feeding have shown that a diet containing wheat to provide 50 percent of the daily calories and 80 percent of the protein, and supplemented with casein to supply the remaining 20 percent of the daily protein requirement supported excellent ponderal and linear growth of children, although plasma amino acid levels indicated that the amino acid lysine was still "first limiting." A diet with 75 percent of calories and all of the protein coming from wheat seemed unable to support adequate growth in most infants. The addition of lysine to correct the low lysine intake made growth adequate in all respects. Potatoes alone were unable to support normal growth in infants. It appears that the amino acid methionine was "first limiting" in potato protein. Four varieties of whole grain sorghum flour (a staple in many underdeveloped countries) exhibited poor protein digestibility, rendering them inappropriate for child-feeding. This work was supported by NICHD.

Work has continued at the Massachusetts Institute of Technology to develop an improved method of assessing protein nutrition status and protein and amino acid requirements, using stable isotope probes (^{13}C , ^{15}H , and ^3H) to quantify whole-body fluxes of indispensable amino acids and their major metabolites. During the past year, this group has found that protein ingestion results in a reduction in the rate of whole-body protein breakdown when a meal that provides adequate energy is consumed. Whole-body alanine synthesis appears to increase with the ingestion of energy-containing meals, suggesting a role for alanine in maintaining whole-body nitrogen economy as well as energy storage. Glycine metabolism, on the other hand,

does not respond to ingestion of an energy-rich meal, although its rate of synthesis is adaptively reduced when protein intake is limited. This work may ultimately provide a better method for the precise estimation of amino acid requirements in individuals than has been available previously.

Current plans include studies concerning environmental and host factors affecting nutritional requirements of the individual. Studies are needed to quantify dietary requirements for essential nutrients known to be limiting in populations living under various ecological conditions, as these may be affected by age, state of human development, sex, and occupation. Specifically, research is needed to determine whether populations living under conditions of chronic environmental and physiological stress can physiologically adapt to lower levels of intake without undue impairment of health and performance.

The Chief of the Department of Nutrition and Biochemistry, Institute of Public Health in Tokyo, visited the laboratories of a number of U.S. nutrition scientists, particularly those of fellow panel members, on behalf of the Japanese Malnutrition Panel. He presented a seminar at NIH on his studies of iron deficiency.

Last year, the Malnutrition Panel held a workshop in Morioka, Japan. The topic was "The Effects of Nutrition on Human Growth and Development and Later Life and Health: Global Priority Issues." The workshop addressed the possible effects of nutritional insults to the young on their subsequent potential to live healthy and productive lives.

Despite previous accomplishments, malnutrition continues to be a widespread problem in Asian countries, except for Japan. Special efforts are being made to increase the amount of collaboration among U.S. and foreign countries in this area. Until the causes and consequences of malnutrition are better understood, continued research is vital to the future of mankind.

U.S.S.R.

The cooperative program in arthritis had its origin in the U.S.-U.S.S.R. Health Exchange Program of 1972, a joint agreement designed to improve collaboration between the two countries in the field of public health and medical science. In September 1973, arthritis research became the fourth major collaborative project in the health sciences in this program.

Through a series of bilateral exchanges of scientific personnel, the program emphasizes clinical studies of the treatment of rheumatoid arthritis and systemic lupus erythematosus. Twelve major meetings have been held between the members of the cooperating centers, and these meetings have been supplemented by the exchange of reprints and lecture materials, as well as by discussions of preliminary results and future projects.

A study of the treatment of rheumatoid arthritis with d-penicillamine at various dose levels was completed in June 1980 with the entry of 100 patients by each side; a final report for the scientific literature is in

preparation. Following a successful, published, descriptive study of juvenile rheumatoid arthritis, a trial comparing hydroxychloroquine to d-penicillamine in that disease was begun in August 1981. Entry of patients into the trial is progressing satisfactorily in both countries. As assessment of the results of total hip joint replacement with artificial joints in both countries has been completed, and a report is in preparation. An agreed-upon assessment of hand function in rheumatoid arthritis is also being conducted in the two countries. Large data sets bearing on the diagnosis of scleroderma have been exchanged and are under discussion.

In the more basic sciences, considerable attention has been devoted to collagen synthesis and degradation using fibroblasts in culture derived from normal persons and patients with scleroderma.

The program is organized into three major areas: clinical studies in rheumatic disease; basic science of rheumatic disease; and orthopedic surgery for arthritis. Projects are in operation in all three.

At the invitation of our Russian collaborators, five American scientists took part in and addressed the International Symposium on Rheumatology sponsored by the All-Union Scientific Rheumatology Society in Tbilisi in October 1980. Our orthopedic area coordinator received a warm welcome and, as the first American ever to do so, addressed an All-Soviet Congress of Orthopedics and Traumatology in Kiev in September 1981. He worked for several months in the collagen laboratories of the University of Pittsburgh.

Visiting Programs

The NIADDK Intramural Program sponsors scientists from many countries under its visiting programs, and in return, intramural scientists from the Institute spend time visiting and collaborating in laboratories and clinics abroad. During the past year, scientists from Israel, India, Poland, Japan, China, the United Kingdom, France, Germany, and other countries have worked in the intramural laboratories and clinics of the NIADDK. This exchange of high-caliber scientists across national boundaries provides vital opportunities for cross-fertilization of new ideas and biomedical techniques. It has been a mutually beneficial mechanism for many years and is expected to continue to provide significant scientific dividends in the future.

Extramural Programs

NIADDK continues to support research by scientists outside the United States as part of its extramural research program. This is done with the award of grants and contracts, approved through the competitive peer review process, to highly qualified investigators exploring problems of high priority. In fiscal year 1981, 46 research grants were awarded to international institutions for a total of \$2,086,212; 12 training grants were awarded for a total of \$96,960; and 7 contracts were awarded for \$648,000. The following sections deal with the efforts of the NIADDK extramural program areas as they relate to the support of international research.

In FY 1981, the Institute's *Diabetes, Endocrine, and Metabolic Diseases Program* supported approximately 37 international research projects in the amount of \$1.9 million. Funds from the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, and the National Institute of Dental Research enabled scientists from all over the world to participate in the Workshop on the Initial Lesion of Insulin-Dependent Diabetes Mellitus (IDDM) held in Reston, Virginia, in November 1980. This workshop gave U.S. scientists and their colleagues from Europe the opportunity to exchange ideas in the area of diabetes and immunology in order to further knowledge regarding the involvement of the immune system in IDDM.

The Diabetes Program is also supporting the forthcoming trial on the relationship between the degree of blood glucose control and emergence of the early vascular complications of insulin-dependent diabetes, which should offer opportunities for international collaboration in several areas:

- Between U.S. and foreign scientists in planning the protocol of the forthcoming study.
- Between the NIADDK clinical trial and an ongoing multinational trial supported by the Kroc Foundation.
- On the clinical trial's Policy and Procedures Advisory Group.

The *Kidney, Urologic, and Hematologic Program* supports five investigator-initiated research grants that are international in scope. A hematologic study about globin gene transcription is being supported at the University of London, England. Two urology grantees are collaborating with foreign scientists in France and West Germany, with funding being divided between NIADDK and foreign institutions. In France, they are conducting studies on steroid receptors in prostatic hyperplasia; in Germany, a cooperative clinical trial is under way to compare the surgical with the medical treatment for vesico-ureteral reflux in children. The Chronic Renal Disease Program is currently supporting two international grants, one in Finland to study kidney

graft rejection, and one in Sweden that concerns the metabolism of proteins, fats, carbohydrates, and salt during continuous ambulatory peritoneal dialysis (CAPD) for chronic renal failure.

Conferences, Seminars, and Meetings

Scientific meetings with an international audience play a major role in scientific communication as they provide a forum for the exchange of research information among investigators from different countries and stimulate scientific collaboration and cross-fertilization. NIADDK continues to support selected conferences with international participation as part of its programs. Examples of the types of conferences supported in part by NIADDK in fiscal year 1981 include:

- Sixth International Congress of Human Genetics.
- International Conference on Peroxisomes and Glyoxisomes.
- Twelfth International Congress of Nutrition.
- Abnormal Hemoglobins: Genetics, and Populations and Diseases.
- International Workshop on Calcium and Phosphate Transport Across Biomembranes.
- Seventh International Biophysics Congress.
- International Diabetes Foundation Committee on Diabetes in Youth.
- Second International Workshop on Bone and Soft Tissue Densitometry.
- International Symposium on Osteoporosis.
- International Symposium on the Contributions of Chemical Biology to the Biomedical Sciences.
- Arachidonic Acid Metabolites and the Kidney.
- Sixth International Symposium on Bioelectrochemistry.
- Thirteenth Annual International Biomaterials Symposium.
- International Workshop on the Initial Lesion of Insulin-Dependent Diabetes Mellitus.
- International Symposium on the Brattleboro Rat.

NATIONAL INSTITUTE OF CHILD HEALTH AND HUMAN DEVELOPMENT

Introduction

The mission of the National Institute of Child Health and Human Development (NICHD) is to conduct and support research on the reproductive, developmental, and behavioral processes that determine the health of children, adults, families, and populations.

The Institute's programs are based on the concepts that adult health and well-being are determined in part by episodes in early life, that human development is a continuous process through life, and that reproductive processes and the management of fertility are of major concern, not only to the individual, but to the whole of society.

The NICHD supports research in the reproductive sciences to develop knowledge to enable men and women to regulate their fertility with methods that are safe, effective, and acceptable to various population groups, and to overcome problems of infertility. In the social and behavioral sciences, Institute-sponsored research is aimed at understanding the causes and consequences of population change. Research for mothers, children, and families is designed to advance knowledge of fetal development, pregnancy, and birth; to identify the prerequisites of optimal growth through infancy, childhood, and adolescence; and to contribute to the prevention and treatment of mental retardation.

The pursuit of new knowledge is basic to the Institute's mission. The NICHD regards international cooperation as a catalyst for the attainment of new knowledge. Through a variety of mechanisms, the Institute has maintained and expanded its activities in the international exchange of scientific information. Activities are conducted under bilateral agreements and the Special Foreign Currency Program (P.L. 480), and in cooperation with international agencies, the NIH Visiting Program, and the Fogarty International Center.

In addition, the NICHD provides direct support to foreign investigators through research grant and contract awards to their home institutions, and indirect support through awards to U.S. institutions having foreign components or involvement in foreign research investigations.

Bilateral Agreements and Other Country-to-Country Activities

Australia

At the University of Sydney in Australia, the NICHD supports a study aimed at characterizing the association between oral contraceptives and malignant melanoma of the skin. The safety of oral contraceptives is of prime importance to users in the U.S. and to the increasing numbers of users throughout the world. Preliminary analyses suggest that the use of oral contraceptives (OC's) increases a woman's risk of developing malignant melanoma of the skin and that the risk further increases with extended use of oral contraceptives. The increased risk was most marked among women who had used OC's for 10 or more years. Still to be determined, however, is the extent to which other factors, such as skin or hair color, and the tendency to burn, blister, or freckle from exposure to sunlight, influence the relationship.

Australian investigators working with NICHD grant support have recently made great strides in understanding the vital role in childbirth of relaxin, a peptide hormone. Relaxin softens and dilates the cervix at the time of delivery and facilitates childbirth by relaxing the pubic ligament. The study, using the pig as an animal model, has purified porcine relaxin, determined the hormone's molecular weight (6,000 daltons), and defined its structure.

India

In accordance with the Indo-U.S. Bilateral Agreement dating from 1974, and in cooperation with the U.S.-India Subcommission on Science and Technology and the India Council for Medical Research, the NICHD staff has participated in meetings to advance collaborative research in the population sciences and in nutrition.

During fiscal year 1981, NICHD conducted a training workshop in New Delhi to teach a group of mid-career Indian scientists the techniques involved in hybridizing antibody-forming cells with certain types of cancer cells and cloning selected hybrids, including developmental biology, genetics, and reproductive biology.

Japan

NICHD supports some research under the U.S.-Japan Cooperative Medical Sciences Program Malnutrition Panel. The panel is concerned with nutritional problems of importance to Asian people. Priority areas and

activities of the panel will be found in the NIADDK section, since NIADDK administers the panel.

Nigeria

During 1981, the Director, NICHD, served on the Subcommittee on Biomedical Research, U.S./Nigeria Joint Task Force, established under the 1980 Memorandum of Understanding, regarding the development of cooperative health activities between the two nations. In September 1981, a formal agreement was signed between the U.S. and Nigeria for cooperation in the field of health.

The NICHD developed a plan for U.S.-Nigeria research collaboration in nutrition, beginning with workshops to develop preliminary research protocols, followed by workshops in the U.S. which will include Nigerian investigators.

People's Republic of China

In January 1979, the United States and the People's Republic of China signed an Agreement for Cooperation in Sciences and Technology. The agreement, containing specific allowances for cooperative activities in a number of scientific fields, was furthered in June 1979 when health officials from both countries signed the Protocol for Cooperation in the Science and Technology of Medicine and Public Health. Areas of cooperation between the NICHD and counterparts in China include human genetics, public health and health services research, child development and nutrition, and reproductive physiology and family planning.

In fiscal year 1981, NICHD staff led and participated in delegations to China in the areas named above. In a November 1980 visit to China, the Director, NICHD, headed the human genetics group and participated in the group on child development and nutrition. In June 1981, the Director, Center for Population Research, NICHD, led the first delegation to China in the field of reproductive physiology and family planning techniques. This visit was concerned only with biomedical research, specifically reproductive biology and contraception. The Director of the NICHD Epidemiology Program, a member of the health services research delegation, took part in a July 1981 workshop in Shanghai. Of particular interest to the NICHD is the development of data regarding the rate of low birth-weight in China, reportedly to be about half the U.S. rate.

In October 1980, a study tour of scientists from China met with NICHD intramural staff to discuss *in utero* diagnosis of genetic disorders.

Representatives from the Chinese Academy of Medical Sciences visited the U.S. between January and March 1981 as guests of the Institute and under the auspices of the human genetics portion of the U.S.-PRC Protocol. They met with NIH scientists and with physicians and researchers across the country.

Programs of cooperation are being developed in many areas, and future commitments consist of continuing discussions and the exchange of information.

Poland

The Fifth Annual U.S./Polish Medical Week, held during October and November 1980 in Bethesda, was

hosted by the NICHD and focused on pediatrics. The visiting delegation was led by representatives from the National Research Institute for Mother and Child, Warsaw, and included pediatricians from various institutions in Poland.

Highlights of the week included grand rounds on "Screening Programs for Inborn Errors of Metabolism in Poland," given by the leader of the Polish delegation and, in cooperation with the Fogarty International Center, a seminar on metabolic and other genetic disorders sponsored by the NICHD. The Polish visitors also attended the 50th Anniversary National Meeting of the American Academy of Pediatrics, which provided the visitors an opportunity for contact with the wider U.S. pediatric community.

The NICHD and Polish representatives agreed to continue the exchange of information and to identify common research interests and areas needing further exploration.

Cooperation with International Organizations

World Health Organization. Members of NICHD staff serve as consultants to the WHO Special Programme of Research, Development and Research Training in Human Reproduction and as members of the WHO Committee on Resources for Research about human reproduction. The NICHD has also provided for the biological testing for long-acting contraceptive drugs synthesized by the WHO contractors.

Pan American Health Organization. Supported by the NICHD, PAHO is studying the effects of opsonin replacement in Guatemalan children with severe malnutrition. Opsonins are special antibodies that coat the cell walls of invading bacteria to bring about their destruction by phagocytic white blood cells. The stimulus for this research stems from the observation of depressed opsonization of bacteria in protein-calorie malnutrition. This opsonin deficiency may play a role in the high incidence of fatal gram-negative septicemia in malnourished individuals.

European Medical Research Council. Staff of the NICHD are members of the Council's Advisory Subgroup on Reproduction, which was established to identify areas of cooperation within Europe and between Europe and the United States on research in reproduction. The subgroup also interacts with the pharmaceutical industry to obtain information about the industry's research projects that might have a bearing on human reproduction.

The NIH Visiting Program and the NICHD Intramural Program. The NIH Visiting Program provides opportunities for recent postdoctoral fellows and senior scientists from abroad to train and to conduct research in the U.S. More than 50 foreign nationals from a dozen countries were involved in the NICHD Intramural Research Program during 1981.

NICHD intramural scientists engage in international collaboration in research projects relevant to their own work at the NIH. For example, studies in this country have shown large doses of vitamin E to be protective against blood cell damage and/or anemia in

patients with certain rare genetic metabolic disorders. In collaboration with the NICHD intramural staff, scientists in Greece have shown that vitamin E significantly reduces the rate of red blood cell destruction in patients with mild anemia from an enzyme deficiency prevalent in the Mediterranean region (Mediterranean G6PD or glucose-6-phosphate dehydrogenase deficiency). Although the vitamin does not correct the underlying defect, the administration of vitamin E does correct the anemia and also reduces the patient's vulnerability to infection. Still to be determined is whether the protection offered by the therapy is sufficient to overcome the severe anemia brought on by drugs or infection.

Extramural Programs

Components of the NICHD extramural research program are the Center for Population Research, the Center for Research for Mothers and Children, and the Epidemiology and Biometry Research Program.

The *Center for Population Research* is responsible for the primary Federal research effort in the population sciences. Included are studies on human fertility and infertility, the development and evaluation of methods of fertility regulation, and the social and behavioral aspects of these problems in relation to individuals and to populations. Through research grants and contracts, the NICHD supports investigators around the world.

In Taiwan, for example, a study of fertility and family planning is examining the demographic transition in that country, assessing the extent and tempo of fertility decline. Particular attention is given to changes in fertility due to changes in patterns of marriage and changes of family planning within marriage. The study has found that despite the widespread use of contraceptives, the decline of the birth rate in Taiwan is probably being slowed because traditional familial forms and relationships are still very important there.

As an indication of the relation between the traditional familial elements and reproductive patterns, the study has found that the length of time a couple lives with the husband's parents, the importance attached to having a male heir, and the expectation of some day living with married sons are all related to lower age at marriage, a large number of births, a higher preferred number of children, and fewer couples using contraception to space their children.

The *Center for Research for Mothers and Children* (CRMC) supports biomedical and behavioral research aimed at making possible pregnancies and births that produce sound infants who can grow to adulthood free of disease and disability. Since its inception, the NICHD has promoted research on the role played by nutrition in the prevention of disease and disability as part of the strategy for achieving that goal.

Current world food policies are largely based on the assumption that if most of the energy needs of humans are satisfied by common staple foods, protein requirements will also be met. This may well be true for adults, but investigators supported by an NICHD grant have shown that this assumption is not true during late

infancy and early childhood in children in Peru.

Bulkiness of staple foods limits amounts that can be consumed. Low protein content and poor digestibility may also limit the amount of utilizable protein available from such diets. For example, when 66 percent of calories is supplied as oats, and oats account for all dietary protein, then weight gain and nitrogen retention are found to be less than when only 22 percent of calories and 50 percent of dietary protein are provided by oats.

Investigators working on this project found a progressive increase in calories, carbohydrate, fat, and nitrogen expelled in the stools when oats supplied 44 percent or more of dietary calories. Results of such NICHD research should influence nutritional programs for infants and children in developing countries.

In addition to the opsonin study cited earlier, the NICHD is currently funding another project in Guatemala to study the relationship between iron-deficiency anemia and behavior in infants. To date, 68 babies between 6 months and 2 years of age, with and without iron-deficiency anemia, have been tested with the Bayley Scales of Infant Development. Both the index of mental development and the index of psychomotor development of the anemic group were significantly lower than those of the nonanemic group.

The investigators also found that in a double-blind, randomized clinical trial, oral iron therapy for 6 to 8 days did not significantly improve the deficient scores of the anemic children.

A group of investigators in Canada is working on a grant from the NICHD to discover new growth factors. Recently, they have found that the human pituitary gland contains a growth-promoting protein in addition to human growth hormone (hGH). The new growth factor appears to be a large protein (40-60,000 daltons) which stimulates rabbit fetal cartilage cells (chondrocytes) to grow in tissue culture. This new growth factor has been named the "pituitary chondrocyte growth factor."

The same Canadian group has also discovered the presence of a growth factor in the cell fluid (cytosol) of specimens of human breast cancer. The factor appears to be a protein which is found in approximately 50 percent of breast cancer specimens, and has been named the "mammary tumor growth factor." This discovery may further the understanding of the cause of the rapid, uncontrolled growth that is seen in many forms of cancer.

The CRMC also supports studies on the human learning process and communicative disorders, especially reading disorders. Compared with speech, reading is not universal. On a worldwide basis, reading is relatively rare; it comes second to speech in the development of the individual, and requires extensive formal instruction. Therefore, information processing in reading depends on the educational methods used to teach reading, and on the particular properties of the language and orthography. NICHD-supported investigators in Yugoslavia are exploiting the special language situation provided by Serbo-Croatian as a means of probing the visual and auditory processing of language

and of comparing the processing of Serbo-Croatian to English.

The *Epidemiology and Biometry Research Program* is collaborating with the Department of Epidemiology at Ben Gurion University, Beer Sheva, Israel, in a study of the effects of westernization on infant feeding practices among Bedouin populations who are undergoing transition from a nomadic to a more settled lifestyle. Data are being developed to test the thesis that as this transition takes place, infant feeding practices shift from long-duration breast-feeding to a combination breast- and bottle-feeding and/or to bottle-feeding exclusively. The effects of these changes on the health of the infants during the first year of life are also under study.

Conferences, Seminars, and Meetings

The Second Indo-U.S. Workshop on Reproduction and Contraception Research was held at NIH in June 1981. Convened in cooperation with the Indo-U.S. Subcommittee on Science and Technology and the Indian Council of Medical Research, the workshop was an intensive working session. In addition to updating various projects previously identified in 1979 at the first meeting in New Delhi, topics for future collaboration were discussed. These areas include the development and testing of new contraceptives and strengthening of capabilities for research in clinical epidemiology, thus broadening the scope of cooperative efforts in reproductive biology.

NATIONAL INSTITUTE OF DENTAL RESEARCH

Introduction

Although rarely fatal, dental diseases are universal and cause untold misery throughout the world. Aware of the severity of the dental problems that plague people everywhere, the National Institute of Dental Research (NIDR) collaborates with international organizations and institutions to stimulate and support dental research and to offer research opportunities to foreign scientists to engage in studies at the Institute's laboratories in Bethesda, Maryland.

Through international scientific cooperation and participation in organizations such as the Fédération Dentaire Internationale (FDI), International Association for Dental Research (IADR), Pan American Health Organization, and the European Organization for Caries Research, the NIDR continues to work to lower the barriers to communication in the field of dental research and to advance dental health everywhere.

The Institute encourages wide exchange of scientific information. *NIDR Abstracts* informs dental investigators of current developments in special areas of interest. This publication is distributed to more than 150 foreign colleagues. Dental scientists around the world have been asked to register their research projects with the Smithsonian Science Information Exchange, and in cooperation with the Exchange, the NIDR annually publishes *Dental Research in the United States and Other Countries*.

Summary of Bid International Programs and Activities

Bilateral Agreements and Other Country-to-Country Activities

Under the auspices of the recently signed agreement on health between the United States and Nigeria, the NIDR is exploring possible collaborative dental research projects.

Activities with International Agencies

The Director serves as a member of the Oral Health Research Advisory Group of the World Health Organization. The Special Assistant to the Director, NIDR, served as a consultant to the USPHS/WHO International Collaborative Study of Dental Manpower Systems in Relation to Oral Health Status (a project officially transferred to the National Center for Health Services

Research) and served as project officer for the Polish replication of that study, which is administered through the Health Resources Administration. The Special Assistant to the Director also served as chairperson for the International Relations Committee of the IADR, and was engaged in projects concerned with the development of dental research capacity in the Third World. NIDR participated in activities of the WHO in Switzerland in connection with the Dental Health Unit and with the Oral Health Research Activity.

NIH Visiting Program

The Institute's intramural program supported or sponsored 28 foreign fellows, 6 visiting associates, and 7 foreign scientists in Bethesda.

Extramural Programs

During FY 1981, the Institute funded 10 foreign grants in the research areas of dental caries, pain control, craniofacial anomalies, and oral soft tissue diseases. Two research fellowships were supported abroad, one in Canada on pain control and one in Denmark on Langerhans cells and oral cancer.

International collaboration during the year continued or was initiated between NIDR scientists and researchers at the following institutions by means of grant support:

- University of New South Wales and the Institute of Dental Research, Sydney, Australia (surface structure of oral bacteria).
- University of Queensland, Australia (surface composition of apatites).
- McGill University, Montreal, Canada (lysosomes in amelogenesis).
- University of Toronto, Canada (brain stem mechanisms and dental pain-trigeminal nucleus caudalis).
- College de France, Paris (migration and differentiation of neural crest cells).
- Gothenburg University, Sweden (plaque control healing after periodontal surgery).
- University of Geneva, Switzerland (revision of the FDI dental lexicon).

Conferences, Seminars, and Meetings

In 1981, 23 NIDR scientists attended and contributed to such foreign meetings as the International Congress on

Thrombosis and Haemostasis, Canada; the annual meeting of the *Fédération Dentaire Internationale*, Brazil; the World Congress on Pain, Scotland; the International Symposium on Glycoconjugates and the Proteoglycan Workshop, Japan; the European and Scandinavian Division of the International Association for Dental Research, The Netherlands; the International Working Group on Mycobacterium Taxonomy, France; and the South African Division of the IADR, South Africa. The extramural program helped to support an international biomaterials symposium held in New York State.

Intramural Programs and Activities

The microbial systematics section of the Institute collaborated with the American Type Culture Collection, the Center for Disease Control, the Food and Drug Administration, the Veterans Administration, the National Oceanic and Atmospheric Administration, and numerous researchers in foreign counterpart organizations to establish a worldwide data bank for information on the diverse strains of human oral microbiota. In addition, NIDR has cooperated with the World Federation of Culture Collections to train microbiologists in developing nations to use computer-compatible methods of data recording.

NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES

Introduction

The National Institute of General Medical Sciences (NIGMS) supports research and research training in basic biomedical fields that undergird disease-specific initiatives of other NIH Institutes. The Institute has supported a number of basic research project grants in six different countries through three of its program areas. Furthermore, although it is not anticipated that NIGMS would set aside funds for international activities in the immediate future, the Institute is ever alert to consider international cooperative projects which might develop and appear to be within its mission, on a case-by-case basis.

Summary of International Programs and Activities

Regular Research Grants

The Institute accepts grant applications that fall within

its mission of support of basic biomedical research from principal investigators at appropriate institutions in foreign countries. Seventeen such grants were awarded during FY 1981 to principal investigators in six countries (Argentina, Australia, Canada, Israel, Spain, and the United Kingdom). These awards were made in the Cellular and Molecular Basis of Disease Program, the Genetics Program, and the Pharmacological Sciences Program areas and totaled approximately \$750,000.

Conferences, Seminars, and Meetings

NIGMS, as the lead Institute, joined other Institutes at NIH to supply foreign travel funds for American scientists to participate in the Sixth International Congress of Human Genetics which was held in Jerusalem, Israel, from September 13 to 18, 1981.

NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES

Introduction

The post-World War II growth in industrial and commercial activities and the acceleration of industrialization in developing countries have shown that while technology has produced tremendous benefits for society, it has also had serious, often unanticipated side effects. Concern for the potentially adverse effects of environmental chemicals on human health and the ecosystem has become worldwide. The National Institute of Environmental Health Sciences (NIEHS) serves as the principal Federal agency for biomedical research on the effects of chemical, physical, and biological environmental agents on human health. The research aims of NIEHS focus on identifying and investigating environmental factors that may have deleterious effects on human health (e.g., mutations, cancer, lung disease, birth defects), on quantifying these effects, on understanding the mechanisms of action of toxic agents on biological systems, and on developing test methods for predicting the toxicity of chemicals. Through the development of these efforts, NIEHS research provides the basic information necessary for establishing disease prevention programs. These goals transcend national boundaries, and NIEHS plays a leading role in the organization and development of international efforts dealing with environmental health problems.

Summary of Bid International Programs and Activities: Bilateral Agreements and Other Country-to-Country Activities

Egypt

Cooperation between American and Egyptian environmental health scientists is being carried out under the auspices of the U.S.-Egypt Joint Working Group on Health Cooperation (JWGHC). NIEHS has been assigned responsibility for the U.S. Subcommittee on Environmental and Occupational Health of the JWGHC.

Efforts to date have consisted of a workshop held in Egypt in early 1980 to identify the biomedical impacts of technology transfer. During 1981, an Egyptian coordinator for this agreement visited the U.S. to discuss proposals for a series of workshops to be held in Egypt in 1982. These workshops will focus on the following

areas: pesticides, trace metals, radiation, environmental management, and mutagenesis.

An information unit for environmental impact assessment is also being established. This project is directed to the needs expressed by the Egyptians for information in the areas of environmental and occupational health. An Oversight Committee will be established to maximize the beneficial effects and to minimize or avoid the potential deleterious effects of technology transfer between the United States and the Arab Republic of Egypt.

The Oversight Committee will provide the administrative and staff functions to prepare technology assessment statements and develop data on the potential health, social, biological, and environmental aspects of the transfer of specific items of technology relevant to the Egyptian people and their environment. The committee will also examine and describe advantages and disadvantages of alternative technologies eligible for transfer.

These activities are funded largely through Special Foreign Currency (P.L. 480) Programs.

Italy

Cooperation between American and Italian environmental health scientists is being carried out under the joint U.S.-Italy Memorandum of Understanding signed by the Secretary, DHEW, and the Italian Minister of Health in 1977. Since that time, there have been several exchange visits by scientists from both sides and discussions aimed at defining areas of joint cooperation. Under discussion are possible collaborative activities concerned with the following subjects: mutagenicity testing; testing of complex mixtures; long-term testing; and quantitative risk assessment.

In addition to these activities, NIEHS staff have been involved in meetings and consultations concerned with the explosion of a chemical reactor in Seveso, Italy, which resulted in exposure of a large population to dioxins.

Japan

Cooperation between American and Japanese scientists on environmental health problems takes place under two formal agreements: the U.S.-Japan Cooperative Medical Sciences Program and the Agreement on U.S.-Japan Cooperation in Research and Development in Science and Technology.

Under the U.S.-Japan Cooperative Medical Sciences Program, American environmental health scientists participate in the Panel on Environmental Mutagenesis and Carcinogenesis chaired by the Associate Director for Genetics, NIEHS. Joint areas of research focus on the detection of mutagenic and carcinogenic chemicals using both *in vitro* and *in vivo* test systems, and on monitoring human populations for evidence of exposure to mutagenic and carcinogenic chemicals. Joint research on carcinogens and mutagens in the diet and dietary tract have been particularly productive.

The 10th Joint Meeting of the U.S. and Japan was held in Kyoto, Japan, in September 1981, and reviewed the information presented at the Third International Conference on Environmental Mutagens, held in Tokyo, September 1981.

Under the U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology, NIEHS participates in the toxicology program area in the counterpart working group on health. Exploratory discussions on cooperation in this program were initiated in 1980 by an exchange of scientists for the purpose of familiarization with the organizations and research programs in this area. In September 1981, the Director, NIEHS, led the U.S. counterpart working group on health at the first meeting of the Joint Committee for the U.S.-Japan Cooperation in Research and Development in Science and Technology, held in Tokyo, Japan. In the toxicology program area, discussions centered on cooperation in the following subjects: development and validation of short-term test methods to detect carcinogens and mutagens; development of methods to test volatile chemicals; development of methods to study mixtures of chemicals; studies on the chemical initiation and promotion of cancer; and the development of approaches to quantitative risk assessment.

In addition to these activities, the Director, Biometry and Risk Assessment Program, NIEHS, continues his collaboration with the Radiation Effects Research Foundation, Hiroshima, to analyze the long-term health effects of atomic bomb victims.

People's Republic of China

Cooperation between the United States and the People's Republic of China in the area of environmental health was initiated during 1980 under the U.S.-PRC Agreement for Cooperation in the Science and Technology of Medicine and Public Health. NIEHS is a participant in the public health and health services research, which includes concerns relating to environmental and occupational health.

Exploratory discussions during a visit to the United States by the Chinese coordinator for this topic centered on cooperation in the following areas: biochemical and epidemiological research related to asbestosis and silicosis; biochemical and epidemiological research related to pesticides; development and validation of short-term test methods to detect and assess carcinogens, mutagens, and teratogens in the environment; the application of standard toxicological test methods and the extrapolation of laboratory animal data to man; the application of modern methodology to the estab-

lishment of industrial hygiene standards, particularly in the coal industry; and the application of modern methodology to the establishment of pollution standards for the general environment.

During 1980-81, an NIEHS/NIOSH delegation visited China to participate in the Meeting of the Second Session of the U.S.-PRC Joint Health Committee and to exchange information on heavy metal toxicology, occupational lung disease, and the status of *in vitro* testing for carcinogenesis in the U.S.

U.S.S.R.

The National Institute of Environmental Health Sciences cooperates with counterpart institutions in the Soviet Union under two formal agreements: the U.S.-U.S.S.R. Medical Science and Public Health Cooperative Agreement and the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection.

Under the U.S.-U.S.S.R. Medical Science and Public Health Cooperative Agreement, NIEHS is the lead U.S. agency for the environmental health priority area. Formal collaboration in environmental health research between the United States and the Soviet Union is in its ninth year. The first year was concerned largely with establishing working relationships and agreeing on areas of joint study. Cooperative research efforts initiated in the second year involved exchange visits by scientists of both countries. Research results developed during the second and third years of collaboration were presented by American and Soviet scientists in the First Joint Symposium in Riga, Latvia, in December 1974. Scientific results from cooperative research during 1975 and 1976 were presented at the Second Joint Symposium, held in Marineland, Florida, in December 1976, and results of research conducted between 1977 and 1979 were presented at the Third Joint Symposium held in Suzdal, U.S.S.R., in October 1979. The proceedings of these symposia were published in both countries. During 1977, 1978, 1979, and 1981, major workshops were held on the following topics: developmental toxicology (Leningrad, November 1977); biological effects of metals (Cincinnati, February 1978); behavioral toxicology (Suzdal, November 1978); and biological effects of physical factors in the environment (Seattle, June 1979; and Kiev, May 1981).

Over 50 scientific papers have been published by American and Soviet scientists on the results of environmental health research conducted under this agreement. In addition, a Russian-English *Glossary of Environmental Health Terminology* was published in both countries to assist communications between scientists.

During 1980-81, exchange visits between Soviet and American scientists under the Health Agreement were conducted in research areas concerned with the biological effects of microwave and low-frequency electromagnetic radiation.

NIEHS also participates in the U.S.-U.S.S.R. Agreement on Cooperation in the Field of Environmental Protection, which is administered for the United States by the Environmental Protection Agency. The Director, NIEHS, serves as DHHS representative to the

Environmental Protection Agreement and cochairman of the working group concerned with the biological and genetic effects of pollution. During 1980-81, exchange visits under this agreement were conducted in research are concerned with the health effects of oil shale technology and the mutagenicity of environmental contaminants. In the area of mutagenesis, joint studies are being conducted to determine the significance of an increased mutation rate among congenitally malformed children in the U.S.S.R.

Activities with International Agencies

World Health Organization

NIEHS staff have been active participants in programs of the World Health Organization (WHO) for a number of years. In 1975, NIEHS was designated as a WHO Collaborating Center for Environmental Health Effects. During 1980-81, the Institute, under the leadership of the Associate Director for Health Hazard Assessment, continued to provide advice and scientific expertise to WHO Headquarters and WHO Regional Offices. Collaboration focused mainly on review of draft documents on new WHO guidelines for drinking water quality, and assessment of human exposure to environmental agents.

In 1979, WHO established the International Programme on Chemical Safety (IPCS), a cooperative undertaking involving WHO, the United Nations Environmental Programme, the International Labor Organization, and their member states. During 1980, NIEHS assumed the function of lead institution within the IPCS for mutagenicity, effects on selected organ systems, and toxicology of selected chemicals. The objectives of the IPCS are to encourage international cooperation in the evaluations of the effects of chemicals on human health and on the quality of the environment; to coordinate chemical testing and toxicological research to eliminate unnecessary duplication of effort; to develop international protocols for laboratory testing, epidemiological studies, and risk assessment; to develop international guidelines and exposure limits for chemicals in air, water, and food and limits for hazardous chemicals in workplaces; to develop response mechanisms for coping with chemical emergencies which may be international in scope; and to promote training and development of manpower in areas and specialties necessary for the achievement of program goals.

The IPCS Advisory Committee met for the second time in December 1980, again under the chairmanship of the Director, NIEHS. The second session of the IPCS Technical Committee, consisting of all the directors of IPCS lead institutions or their representatives, was held in Geneva in February. In October 1980, a cooperative agreement was signed between NIEHS and WHO, to include such activities as international evaluations of biological effects of chemicals and health hazard assessments, and review and/or validation of methods for testing of mutagenicity, carcinogenicity, neurobehavioral toxicity, and toxicity to reproductive function. In September 1981, the agreement was extended for another year. In order to assist NIEHS participation in

the IPCS, a WHO Interregional Research Unit was established at NIEHS in 1981.

Within the framework of IPCS, NIEHS' Office of Health Hazard Assessment is responsible for three projects: preparation of a draft document on biological effects of 2,6-toluene diamine; preparation of a similar document on phthalic acid esters; and scientific editing and updating of the second volume of a WHO monograph on Principles and Methods for Evaluating the Toxicity of Chemicals. Also, within the framework of IPCS, NIEHS staff participated in and chaired several planning meetings, held in Geneva during 1981, to develop international protocols for testing for mutagenicity, neurobehavioral toxicity, and reproductive toxicity.

NIEHS staff also participated in a Workshop on Methods for Assessing the Effects of Chemicals on Reproductive Functions, organized by the Scientific Group on Methodologies for the Safety Evaluation of Chemicals (SGOMSEC) in May 1981 in Ispra, Italy. SGOMSEC is one of the IPCS projects implemented in collaboration with the Scientific Committee on Problems of the Environment of the International Council of Scientific Unions (SCOPE/ICSU) in May 1981.

In other WHO activities, the Chief of the Laboratory of Reproductive and Developmental Toxicology continued his role as temporary adviser to the Toxicology Review Panel of the WHO Special Programme of Research, Development, and Research Training in Human Reproduction. The review panel meets twice a year to consider the potential toxicity associated with current and future approaches to contraception. An NIEHS Visiting Scientist served as a WHO temporary adviser in Geneva to assist in the final scientific editing of the environmental health criteria document on arsenic. The Associate Director for Genetics, and the Head, Environmental Mutagenesis Test Development Program, participated in the WHO Consultation on Genetic Monitoring for Environmental Effects, Ottawa, Canada, October 17, 1980. The purpose of the consultation was to discuss how to evaluate effects of exposure of individuals in the human population to mutagens.

Health Scientist Exchange Programs and NIH Visiting Program

During 1980-81, collaborative research activities were carried out in the intramural laboratories by 53 Visiting Fellows and Scientists. They came from Australia, Belgium, Canada, England, Finland, France, Hungary, India, Japan, Korea, New Zealand, People's Republic of China, Sweden, Switzerland, Taiwan, West Germany, and Yugoslavia.

Collaborative research projects included studies on: mutagenicity test methods; biometry and quantitative risk assessment; mechanisms of carcinogenicity; pharmacokinetics and liver metabolism; neurobehavioral, pulmonary, and reproductive toxicity; and the effects of noise and physical factors on the nervous system.

Two WHO fellows from the People's Republic of China are currently receiving training in the Institute's Laboratory of Pulmonary Function and Toxicology.

Extramural Programs

Through its extramural program, NIEHS provides support to the State University of Leiden, The Netherlands, to study the induction of genetic damage by chemical mutagens; the University of Western Ontario, London, Canada, to study the nature of lead-binding and mercury-binding nuclear proteins; the University of Turku, Finland, to study gastrointestinal and pulmonary metabolic functions; the State Agricultural University, Wageningen, The Netherlands, to study chemically induced nondisjunction in mutant mice; and Tel Aviv University, Israel, to study hydrocarbon recognition in petroleum-degrading bacteria.

Conferences, Seminars, and Meetings

In order to provide an opportunity for scientists from different countries to exchange research results and stimulate scientific collaboration, NIEHS continues to support a number of conferences with international participation as part of its programs. Examples of the types of conferences supported in part by NIEHS this past year include:

- Symposium on Molecular and Cellular Mechanisms of Mutagenicity.
- Statistical Analysis of *In Vitro* Test for Mutagenicity.
- Conference on Phthalates.
- Symposium on Lung Neuroendocrine Cells and Regulatory Peptides.
- Target Organ Toxicity: Immune System.
- International Lead Conference on the Effects of Lead Exposure on the Behavior of Children.

Intramural Programs and Activities

NIEHS scientists from various intramural laboratories continue to collaborate on an informal basis with scientists from a number of nations. The Chief, Comparative Medicine Branch, continues to be a charter member of the International Committee on the Wasting Marmoset Syndrome (WMS). The committee was chartered in 1978 by the Division of Research Resources of NIH, and includes participants from Australia, Brazil, The Netherlands, Peru, the United Kingdom, the U.S., and the U.S.S.R. The WMS bears resemblance to protein-calorie deficiency in man, and the current focus of attention is on a nutrition causation.

The Chief, Laboratory of Biochemical Genetics, serves as a committee member of the International Commission for the Protection Against Environmental Mutagens. Two NIEHS scientists participated in a Latin American Course on Genetic Toxicology which was held in Mexico City, Mexico, in August 1981, for the purposes of developing new methods of identifying potential mutagens and carcinogens; offering a comprehensive and balanced view of the field of genetic toxicology; stimulating multidisciplinary investigation of the effects of environmental contamination; and defining particular strategies for the study of environmental problems in Latin America.

Laboratory of Environmental Biophysics scientists participated in the International Symposium of Spin

Trapping and Nitroxyl Radical Chemistry at the University of Guelph, Canada, July 16, 1981. In June 1981, NIEHS also collaborated with the University of Buenos Aires, Argentina, on the free radical metabolism of nifurtimox, a nitrofurantoin used in the treatment of Chagas' disease.

The Chief, Laboratory of Environmental Chemistry, participated in a Workshop on Dioxins and Related Compounds in Rome, Italy, October 1980. Two NIEHS scientists are also collaborating with the Department of Pharmacology, University of Urbino, Italy, on the development of a radioimmunoassay capability for dioxins applicable to the Seveso, Italy, dioxin contamination problem. This methodology, developed in NIEHS laboratories, is under consideration for adoption by the American Society for Testing and Materials as a standard method. Another NIEHS scientist was invited to give the plenary lecture to the British Society of Mass Spectrometry in Cambridge, England, September 1981. Collaborative research efforts, which are determining the stereoselectivity of the enzymatic reaction between glutathione and styrene oxide, continued between the Laboratory of Pharmacology and Hebrew University, Israel. NIEHS is also collaborating with Hebrew University on the toxicity and metabolism of the trichothecene mycotoxin, T-2 toxin. A Laboratory of Pharmacology scientist is continuing his collaborative research efforts with scientists at the Medical School in Dundee, Scotland, in which the effects of hormone administration on the perinatal development of xenobiotic-metabolizing enzyme systems are being studied.

Collaborative research is continuing between the Laboratory of Reproductive and Developmental Toxicology and the Institute of Pharmacology and Toxicology, University of Wurzburg, Federal Republic of Germany. Scientists in both institutions are studying the target organ metabolism and bioactivation of the carcinogenic estrogen, diethylstilbestrol (DES). Such studies should provide new insights into mechanisms of hormonal carcinogenesis.

Interagency Activities

NIEHS continues to support the Environmental Mutagen Information Center at the Oak Ridge National Laboratory by interagency agreement. The center works closely with investigators around the world in both obtaining and supplying information on environmental mutagenesis. The center has over 30,000 bibliographic entries in its data banks and remains a unique worldwide resource for information in the area of environmental chemical mutagenesis.

NIEHS has also established the Environmental Teratology Information Center in collaboration with the Department of Energy and the Oak Ridge National Laboratory. Information on teratogenesis is collected, indexed, and made available to the biomedical community directly from the center or the National Library of Medicine's TOXLINE. The center is a unique worldwide resource for information in the area of teratology.

NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE

Introduction

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) serves as the segment of NIH responsible for basic and clinical research on disorders of the nervous system and of human communication. Through its research grant program, application of Public Law 480, which permits use of U.S.-owned funds in the currencies of certain countries, and collaborative research projects engaging NINCDS scientists and their foreign colleagues, the Institute maintains continuing interaction with neuroscientists internationally. The neurological and communicative disorders are major problems in virtually every country of the world, and all nations stand to benefit from international research efforts and exchange of knowledge. Furthermore, some of the neurological disorders vary in incidence and severity from country to country. Study of these variations, and uncovering of their causes, can be expected to lead to clearer understanding of the causes of the disorders themselves. The potential impact of international neuroscience research is therefore very great.

Summary of Bid International Programs and Activities: Bilateral Agreements and Other Country-to-Country Activities

In FY 1981, NINCDS participated in no bilateral agreements. Negotiations were initiated with the Government of Italy for epidemiological studies of stroke and the dementias.

Egypt

Two Egyptian projects were conducted on perinatal screening of developmental malformations and the venoms of poisonous snakes. In the perinatal screening project, over 10,000 patients in Cairo and Mansura have now been studied, and the project has revealed a higher-than-normal incidence of spina bifida and anencephaly. Data from this project are undergoing a comprehensive analysis to see if the reasons for the higher incidence can be determined. The snake venom study, involving collection of venoms from North and

East Africa as well as Egypt, has resulted in the publication of six scientific papers in journals outside of Egypt, and has put the Egyptian Government in a position to manufacture good antivenins for North and Central Africa.

Poland

In 1981, NINCDS had four P.L.-480 projects funded at a total annual level of \$269,000. Two in Poland were concerned with neuromuscular disorders: a study of the role of neuroglial cells in the processes of myelination and demyelination, and a study of the degree of muscle lesion in different disease conditions, and the connection between endocrine and muscle disturbances. The Polish groups, located at the Medical Academy of Warsaw and at the Medical Academy in Poznan, have access to virtually all cases of neuromuscular disease in Poland, and are a valuable international research resource.

Activities with International Agencies

World Health Organization

Since 1975, the NINCDS has been one of eight WHO Collaborating Centers in the Neurosciences. These centers, positioned strategically throughout the world, further international research efforts on neurological disorders and initiate and demonstrate community programs for prevention and treatment of these disorders. Special emphasis is being given to the cerebrovascular disorders (stroke), the convulsive disorders (epilepsy), and the neurological and communicative disorders aspects of nutritional and developmental problems of children. The other seven WHO Collaborating Centers in the Neurosciences are:

- The Instituto Nacional de Neurologica, Mexico City, Mexico
- The Montreal Neurological Institute, Montreal, Canada
- The Groupe Hospitalier de la Timone, Marseilles, France
- The University of Geneva, Geneva, Switzerland
- The University of Ibadan, Ibadan, Nigeria
- The Academy of Medical Sciences of the U.S.S.R., Moscow, U.S.S.R.

●The Nair Hospital and TN Medical College, Bombay, India

Each center funds its own activities and includes collaborative research, publications for scientific information exchange, support of conferences and courses, advisory services and technical assistance, and training.

Health Scientist Exchange Programs and NIH

Visiting Program

During FY 1981, the NINCDS Intramural Program hosted 80 Visiting Scientists, Visiting Associates, and Visiting Fellows from 32 other countries. Countries represented were:

Argentina	Japan
Austria	Korea
Belgium	Mexico
Bolivia	Netherlands
Brazil	Nigeria
Canada	People's Republic of China
Denmark	Philippines
Finland	Poland
France	Sierra Leone
Greece	Spain
Hong Kong	Sweden
Hungary	Syria
India	Taiwan
Iran	Turkey
Israel	United Kingdom
Italy	Yugoslavia

The contributions of these workers add immeasurably to the strength and effectiveness of the NINCDS Intramural Program, and the experience and new knowledge they take back with them to their home countries strengthen the neurosciences around the world.

Extramural Programs

NINCDS funded 13 foreign research grants in FY 1981, totaling \$1,798,546. Grants were awarded to institutions in Canada, Israel, England, Sweden, Italy, and Mexico. These grants are for both clinical and basic research, and have been awarded to outstanding investigators exploring problems of high priority in the U.S. and in their own countries.

The largest NINCDS foreign grant in 1981 was to the University of Western Ontario for the gathering and analysis of data from approximately 60 U.S. foreign medical centers on the effectiveness of a surgical procedure for preventing strokes. The procedure, involving grafting of a scalp artery to an intracranial artery to improve blood supply and known as the extracranial/intracranial bypass, is widely practiced but not statistically proven to be better than other forms of treatment. By 1983, the results of this study will be available to neurosurgeons and stroke specialists in all countries.

NINCDS, the Fogarty International Center, and the WHO jointly sponsor a Neurosciences Fellowship Program. This program provides men and women from

developing countries with stipend support for advanced training in the U.S. to prepare them for leadership roles in academic and public health careers in the neurosciences in their own countries. In 1981, NINCDS supported three international neurosciences fellows, two at NIH from the People's Republic of China, and one at UCLA from the Philippines.

Conferences, Seminars, and Meetings Sponsored by NINCDS

In November 1980, NINCDS sponsored an international meeting in Los Angeles on status epilepticus. The meeting resulted in formulation of guidelines for emergency room treatment of status epilepticus, and confirmed the potential usefulness of Lorazepam, a drug now undergoing development, which may improve the treatment of status epilepticus.

Intramural Programs and Activities

NINCDS' intramural work in epilepsy drug development has been greatly enhanced by collaboration with European drug firms, and in some cases, other foreign investigators. In 1981, this work continued, using progabide, an experimental antiepileptic drug manufactured by a firm in France. NINCDS scientists also completed planning for a pilot study of flupertine, an experimental antiepileptic drug manufactured in West Germany.

The extensive international collaborative work of the NINCDS Laboratory of Central Nervous System Studies on the slow, latent virus-induced brain disorders such as Creutzfeldt-Jakob disease and on Korean hemorrhagic disease and related disorders, which are endemic in Asia and portions of Europe, continued in 1981.

Part of this work is being carried on at a field research center established on Guam where a form of amyotrophic lateral sclerosis (ALS) is over 100 times more common than in the continental United States. Field surveys to obtain materials for further serologic, hematologic, neuropathologic, and genetic studies are being conducted. Originally, ALS was thought to be a genetically determined, inherited disease, but mounting evidence seems to indicate that some environmental factor may be responsible. Extensive analyses of family histories in a village (Umatac) where prevalence is extremely high are nearing completion.

Discovery of a second focus of the disorder in the Kii Peninsula of Japan has heightened NINCDS efforts, in cooperation with other scientists, to ascertain the pattern of ALS distribution in the West Pacific islands and to evaluate as far as possible all suspicious environmental factors, including geographic, socioeconomic, dietary, and occupational features. An abnormally high incidence of Parkinsonism-Dementia Complex (a form of progressive extrapyramidal disease) has also been noted in this region. These and other neurosensory disabilities are under investigation in this unique environment.

NATIONAL LIBRARY OF MEDICINE

Introduction

The International Programs of the National Library of Medicine (NLM) are a natural extension of NLM's domestic responsibilities. These activities are cooperative in nature and have relevance to both the developed and developing world. This past year has seen a continuation of the international MEDLARS agreements with the addition of a new center in Colombia; the continuing assessment of the NLM experimental program with the World Health Organization for the provision of services to developing countries; continuation of the NLM publications exchange program; the implementation of a cooperative program with the People's Republic of China; the production of critical reviews under the Special Foreign Currency Program; and specialized training for colleagues from abroad.

Biomedical and health information is essential for the advancement of biomedical research, education, and the provision of health care. The recognition of this is evident in the international technical bilateral arrangements of NLM and the use of the MEDLARS system in many corners of the world. The mechanisms may be through on-line networks, linking the user to the computer system, or through NLM publications. The latter may be comprehensive, such as *INDEX MEDICUS*, or may be specialized, such as the *Quarterly Bibliography of Major Tropical Diseases*, but all serve the needs of the health professional.

International MEDLARS Agreements

The agreements for access to NLM's MEDLARS system are technical arrangements that are *quid pro quo* in nature. The cooperating country designates an institution to serve as a national biomedical and health information resource. In return for MEDLARS tapes or telecommunications access to NLM's computer, the cooperating country performs or funds services to be provided to NLM.

The new MEDLARS center at Colombia was established in 1981. The participating organizations in Colombia are the FUNDACION OFA para el Avance de las Ciencias Biomedicas and the Fondo Colombiano para Investigaciones Cientificas y Proyectos Especiales (COLCIENCIAS). FUNDACION OFA has as its objectives the improvement and accessibility of information

for the biomedical professions and the improvement of the quality of education in the health sciences. An agreement was also reached between the National Library of Medicine and the Ministry of Health of Kuwait for the future implementation of a MEDLARS arrangement.

Cooperation with the Chinese Academy of Medical Sciences

The National Library of Medicine has a cooperative *quid pro quo* arrangement with the Institute of Medical Information, Chinese Academy of Medical Sciences. This arrangement was implemented in February of this year with the arrival of two Chinese scientists to work for approximately 5 months on the Chinese traditional medical literature in the collection of the NLM. The scientists identified, verified, and described almost 900 items in such a way that the information is entered in the cataloging records and the computer system of the National Library of Medicine and made available to scholars. In return for their work on NLM's Chinese literature collection, the Library will provide two Chinese with training in modern medical library management and indexing.

These two scientists brought special expertise to this task. One is an internist at the Capital Hospital (formerly Peking Union Medical College) of the Chinese Academy of Medical Sciences. Her experience has been in clinical work, teaching, research, and medical administration. She has been active in cooperative research programs which have combined both traditional and Western medicine.

The other is a traditional Chinese medicine physician who is currently an Associate Research Fellow in the Department of Medicinal History and Literature of the Academy of Traditional Chinese Medicine. He has conducted research in Chinese medical history, the history of acupuncture and moxibustion, the history of Chinese materia medica, and ancient Chinese medical literature. He has been also a professor at the Advanced School of Traditional Chinese Medicine in Beijing, a member of the Editorial Committee of the *Journal of Traditional Chinese Medicine*, and was formerly Editor-in-Chief of the *Chinese Quarterly of Acupuncture and Moxibustion*. He has also conducted research on histor-

ical relics, including ancient scrolls, medical instruments, and medical stones.

Special Foreign Currency Program

The Library's Special Foreign Currency Program, authorized by Public Law 83-480, as amended, made 21 new awards during FY 1981. Under this program, appropriations of U.S.-owned local foreign currencies are available for scientific writing projects in cooperating countries, including Egypt, India, Israel, Pakistan, Poland, and Yugoslavia. The program is also currently funded through collaborative, bilateral agreements in Israel and Poland. This program enhances the Library's ability to procure and disseminate published information which is important to the progress of biomedical sciences and public health, using foreign scientific personnel and resources.

The projects are multiyear; during FY 1981, there were 89 active projects, totaling an equivalent of \$1,202,123 in foreign currencies. More than 50 percent of the program is currently carried out in Egypt and Poland; about 20 percent is carried out in India. New critical reviews and monographs in health fields constitute 45 percent of the projects; foreign translation projects represent another 28 percent. Of these 89 active projects, 25 are translations from Russian, and 11 from German.

Included among the projects in the six cooperating countries are the preparation of critical reviews of biomedical research and practice; the translation of significant current and historical monographs in the biomedical sciences; publication of major international symposia and conference proceedings; and publication of authoritative bibliographies and other literature tools in special public health fields. These projects span a very broad subject range, with some of the major areas being history of medicine; cancer; heart disease; psychology; and physiology. Examples of new projects activated in FY 1981 include a translation of a Russian study on the neurophysiological investigation of a systems mechanism of behavior; a historical study, by a leading Egyptian scholar, of the health of the pharaohs; and the publication of a bibliography on ticks and tick-borne diseases.

Among the studies published in FY 1981 under this program was *The Effects of Various Diseases on the Development of Atherosclerosis* (New York, Pergamon Press, 1981). This book is the second major translation produced under the collaboration on cardiovascular disease within the U.S.-U.S.S.R. joint program and the NLM Special Foreign Currency Program. It presents original research on atherosclerosis conducted in the Soviet Union. The book was edited by a Harvard Medical School scientist, and printed in India. Another significant study is *Tissue Neuropathology on Viral and Allergic Encephalitis* (Warsaw, Poland, 1980). Distributed through the National Technical Information Service (NTIS), this book is a critical review of the world literature on the pathomorphology of viral and allergic encephalitis, with some emphasis on those types of encephalitis with which the late author worked personally in Poland as founder and director of the Depart-

ment of Comparative Neurology at the Polish Academy of Sciences.

World Health Organization

The National Library of Medicine and the WHO Special Program for Research and Training in Tropical Diseases continued to cooperate in the publication of a *Quarterly Bibliography of Major Tropical Diseases*. NLM produces this bibliography from the MEDLINE system, and WHO distributes approximately 5,000 copies to scientists in institutions in tropical countries. The diseases included in the bibliography are those identified by WHO for special attention: filariasis, leishmaniasis, leprosy, malaria, schistosomiasis, and trypanosomiasis.

An experimental program was continued between NLM and WHO for the provision of MEDLARS searches and interlibrary loans (photocopies of journal articles) to developing countries of the WHO Regions of Africa, Southeast Asia, the Eastern Mediterranean, and the Western Pacific. Under these arrangements, WHO has supported the equivalent of one and one-half people in residence at NLM. The level of activity is modest and it does respond partly to existing needs. However, it also emphasizes that developing countries continue to have significant requirements for biomedical and health information which remain unsatisfied.

Pan American Health Organization

The National Library of Medicine's Assistant Director for International Programs serves as a member of the Scientific Advisory Committee for the PAHO Regional Library of Medicine (BIREME). Located in São Paulo, Brazil, BIREME is unique in the world as a regional resource. BIREME responded to 43,000 interlibrary loan requests, provided services from its subset of the MEDLINE database, held two training courses for Latin Americans, produced a Latin American *INDEX MEDICUS*, and fostered networking within Brazil and among Latin countries.

NLM MEDLARS Centers

Tapes	Tapes/Software	On-line NLM
Germany*	Australia	Canada
Japan	PAHO	Colombia
	Sweden*	France
	United Kingdom*	Italy
		Kuwait**
		Mexico
		South Africa
		Switzerland

* Supplemental on-line access.

** Agreement signed but not operational.

Visitors and Specialized Training

The National Library of Medicine continues to receive about 1,000 international visitors yearly. These indi-

viduals represent both developed and developing countries, and their interests include biomedical and health research, medical education, health care information, library science, biomedical and health

information programs, and the establishment of national resources. Formal delegations were received from France, India, Nigeria, the People's Republic of China, and Sweden.

CLINICAL CENTER

Introduction

The Clinical Center (CC) was authorized by Congress to provide high-quality patient care necessary to conduct biomedical research. The 546-bed hospital has facilities and support services for nearly 1,000 physicians who conduct clinical research for 8 of the 11 NIH Institutes and for the National Institute of Mental Health (NIMH). It was specially designed to place patient care facilities close to research laboratories to promote the quick transfer of new findings of basic and clinical scientists to the treatment of patients. Institutes admit to their units only those patients (upon referral by their personal physicians) who have the precise kind or stage of illness under investigation by scientist-clinicians.

The Clinical Center ensures the highest possible level of medical care to each patient; provides optimal resources and facilities for clinical research; performs research on methods and systems involved in patient care and study; disseminates information to professionals and to the public relevant to clinical investigation; develops and maintains training programs in the techniques and ethics of biomedical and clinical research; and interacts with scientists and physicians, nationally and internationally, on mutual problems of clinical research such as policy, education, ethics, and priorities.

Intramural Programs and Activities

Two scientists from the National Institute of Child Health and Human Development (NICHD) have been involved in a project over the past 4 years, in collaboration with scientists at the University of Athens, the Ben Gurion University School of Medicine in Be'er Sheva, Israel, and the Share Zadek Hospital in Jerusalem, Israel, to evaluate the use of vitamin E as an oral antioxidant in hereditary disorders of red cell metabolism with increased susceptibility to oxidant stress. The primary focus of this project has been on glucose-6-phosphate dehydrogenase (G6PD) deficiency, a disorder prevalent among both Mediterranean and African populations which affects approximately 300 million people on a worldwide basis. Individuals with this disorder are subject to mild chronic hemolysis and acute episodic hemolysis which may often be life-threatening. In addition, G6PD deficiency may cause

jaundice during the neonatal period which may require exchange transfusion and may affect subsequent neurologic development of individuals with this genetic disorder.

Two other scientists, one a Belgian pediatrician and the other a clinical chemist, have collaborated on defining the role of one form of creatine kinase as an indicator of myocardial injury and as a tumor marker. Their goal is to determine what clinical value, if any, there is for the creatine kinase in diagnosing acute myocardial infarction, and as a marker for cancers involving tissues containing it. They have looked in particular at lung, prostate, and colon cancer. This form of creatine kinase may turn out to contribute to the management of patients in these two areas.

Bilateral Agreements and Other Country-to-Country Activities

Reciprocal visits of Soviet and Japanese physicians and scientists occurred during the past year. These were part of international programs for exchange of information relating to blood transfusion and viral hepatitis and for establishment of cooperative scientific studies. A study of viral hepatitis markers in Soviet and American blood donors was recently published as a result of this cooperation.

Health Scientist Exchange

A Visiting Scientist has been brought to NIH under guidelines for expert consultants. He is an established expert in the area of viral hepatitis and brings to the Blood Bank immunologic and biochemical knowledge and skills not otherwise available. His studies are aimed at developing a detection method for the non-A, non-B virus. This virus now accounts for over 90 percent of posttransfusion hepatitis (PTH) cases. A sensitive system for detecting the non-A and non-B virus in asymptomatic blood donors could dramatically decrease the incidence of PTH, a disease which now occurs in approximately 300,000 blood recipients per year.

Conferences, Seminars, and Meetings

The Blood Bank has helped organize and sponsor the 1981 International Symposium on Viral Hepatitis held

in New York City in March 1981, and cosponsored the Second Conference on Regulation of Hemoglobin Switching and a Conference on High Altitude Polycy-

themia. The latter sponsorship emanated from previous Blood Bank studies on high altitude disease, which were conducted in Peru.

DIVISION OF COMPUTER RESEARCH AND TECHNOLOGY

Introduction

The Division of Computer Research and Technology (DCRT) was established in 1964 to make the use of computational methods a tool for the NIH biomedical community. Over the years, the work of the Division has become an integral part of the conduct and management of NIH research programs. At the same time, DCRT has grown to become the largest biomedical computing facility in the world. DCRT staff members continue to create still more powerful and useful systems. Their challenges lie in building strong intellectual links from computers, mathematics, and engineering to the substance of science and the art of administration.

Summary of Bid International Programs and Activities

Four foreign scientists worked at the Division during FY 1981: two from Israel (Physical Sciences Laboratory), one from Belgium (Laboratory of Applied Studies), and one from Mexico (Laboratory of Statistical and Mathematical Methodology).

In addition, the Division cosponsored, with the European Society of Cardiology and others, Computers in Cardiology. This annual conference provides a forum for physicians, engineers, and computer scientists to exchange scientific information on the design and application of computer systems to the field of cardiology.

DCRT staff members informally collaborated with scientists from foreign countries including Australia, Scotland, Japan, France, Canada, Switzerland, Ghana, Greenland, and Singapore. Examples of these international collaborations included:

- Computer-Aided Analysis of Electrocardiograms
Glasgow Royal Infirmary, Glasgow, Scotland
- University of Liege, Belgium

P. L. Medical Service Department, Osaka, Japan
Centre du Médecine Préventive, Nancy, France

- Analysis of Coupled Transport and Biochemical Kinetics

Université de Technologie, Compiègne, France

- Automated Data Processing of Medical Language Mexico

- Multivariate Statistical Analysis

University of Western Australia, Nedlands, Australia

Flinders University, Adelaide, Australia

- Computer Support for Flow Microfluorimetry/Cell Sorters (FMF)

Sites in Europe and Australia

- Chinese Personalities and Institutions in Biomedicine
Fogarty International Center project for the People's Republic of China

- Theory and Measurement of Intermolecular Forces
Guelph University, Guelph, Ontario, Canada

- Theory of Biochemical Separation Techniques
University of Sydney, Sydney, Australia

- Quantitative Analysis of the Electronmicroscopy of Cells and Their Plasma Membranes

University of Geneva, Geneva, Switzerland

- Multivariate and Univariate Forecasts for Blood Constituents

Health Maintenance Program, Japan

- Seroepidemiology Data Processing System

Scientists in Ghana, Greenland, and Singapore

Foreign scientists from West Germany, France, Japan, and the People's Republic of China came to DCRT to draw upon the expertise of its computer scientists. The American Association for the Advancement of Science brought a delegation of international representatives from the Philippines, the Soviet Union, and Hungary for a look at the establishment of the facility for biomedical computing at NIH, as a model.

DCRT supported, and its scientists took part in, several international conferences and meetings during FY 1981.

DIVISION OF RESEARCH RESOURCES

Introduction

Most international activities of the Division of Research Resources (DRR) fall under the Animal Resources Program (ARP), which has the overall objective of supporting resource projects that provide or enable scientists to use animals effectively in human health-related research. Special attention is given to animal resource activities that are broadly supportive of the missions of the various NIH Institutes. The objectives are accomplished through the Primate Research Centers Program (PRCP) and the Laboratory Animal Sciences Program (LASP). Both of these programs, either directly or through grants, are internationally involved in various facets of primatology interest.

Summary of Bid International Programs and Activities: Activities with International Agencies

The Simian Virus Reference Laboratory at the Southwest Foundation for Research and Education, San Antonio, Texas (LASP grantee) has been designated by the World Health Organization (WHO) as a Collaborating Center for Reference and Research in Simian Viruses. The primary purposes of this laboratory are: to prepare, test, evaluate, and standardize simian virus reagents; to provide definitive virus diagnostic services, including identification and characterization of viruses that may be present in primate tissues; to provide consultation services and encourage pooling of information and exchange of organisms among primate centers and other health organizations; and to train interested students in virological laboratory procedures associated with primate investigations.

Extramural Programs

ARP supports a project which studies important habitat features of West African rain forest primates. This project involves a detailed examination of the relationship between feeding behavior, specific ecological conditions, and social organization. It is essentially a predictive study, in which such important variables as foraging styles, diet selection, home range, group size patterns, population density, distribution, and social

interaction are expected to relate in specific ways to ecological conditions. The information will be useful, not only to behaviorists, sociologists, and botanists, but also to conservationists and those making decisions about the size of forest areas in Africa that are necessary to maintain wild populations of primates.

ARP supports a project in northern India focused on population studies of nonhuman primates. The project, begun in 1959 (supported by ARP since 1973), has provided data regarding population dynamics and demographic and reproductive parameters of a natural rhesus monkey population. Within the study, population declines of 71 percent (up to 1977) were noted in an unprotected cohort while a semiprotected cohort increased 186 percent in the same period. Ongoing studies will provide data on the effects of the current export ban of rhesus monkeys from India, habitat displacement which is occurring with one study group, and the feasibility of intentional transplants and relocation of breeding groups. Such information is necessary as a guide to conservation and management of rhesus monkeys and will be important in evaluating the potential supply of rhesus monkeys for biomedical research.

PRCP partly supports a project for the Kutai Research Station in Indonesian primate conservation methodology. Surveys of the natural populations of primate species have been conducted, and training in conservation methods has been provided to ensure the continued availability of supplies of *Macaca nemestrina* and *Macaca fascicularis* for use in biomedical research.

The Institute of Primate Research of the National Museums of Kenya, conceived many years ago by the late anthropologist Dr. Louis Leakey, has recently achieved the status of a Kenyan International Primate Research Center. PRCP provides partial support for its program which consists of the following activities: baseline studies on African primate species; development of primate models for atherosclerosis research; infectious diseases research; coordination of primate field studies; and collaborative research with Kenyan and foreign scientists. The center's overall goal is to contribute to knowledge about East African primate species while fulfilling research needs of Kenya and other countries. The center is being relocated to a new 100-acre site near Nairobi, where construction of facilities is currently underway.

DIVISION OF RESEARCH SERVICES

Introduction

Through collaboration and cooperation with national and international organizations, the Division of Research Services (DRS) plans and conducts centralized programs of scientific, engineering, and technical services in support of biomedical research activities. Professional and technical staff members consult with research scientists during all stages of a research project for the development and use of essential products and services. DRS personnel provide specialized assistance and services in biomedical engineering and instrumentation design and development; research animal production, maintenance, procurement, and animal disease identification and control; biomedical library and translation services; and medical arts and photography.

DRS is involved internationally in such issues as developing a primate supply program for biomedical research; establishing training programs in conservation and management of wild primates; supplying organizations and institutions throughout the world with genetically defined rodents as nuclei for colony development; sponsoring the development of methods for primate population studies and surveys; and initiating programs to train scientific instrument technicians and to establish repair and maintenance centers.

Bilateral Agreements and Other Country-to-Country Activities

Egypt

The Biomedical Engineering and Instrumentation Branch (BEIB) is cooperating in two projects with the Egyptian Government to improve Egypt's capability to repair scientific and hospital equipment.

The first project, funded by the United States Agency for International Development (USAID) with the Egyptian Academy for Scientific Research and Technology, is to establish repair and maintenance facilities at five Egyptian universities. During the first phase of this project, which will end January 31, 1982, BEIB has assisted in the design of the individual repair centers, trained administrative personnel, fully equipped each center, and trained a few personnel for each center in the repair and maintenance of scientific and hospital equipment. During the second phase of this project, BEIB will assist the Egyptian Government in

developing a self-sustaining program in Egypt for the training of repair and maintenance personnel and the development of a nationwide program for the repair and maintenance of scientific equipment.

The second project, funded by USAID and Special Foreign Currency Program funds, is with the Egyptian Ministry of Health. This project, which is at its mid-point, is to establish a prototype repair and maintenance program for an Egyptian governorate which will be used as a model for other programs to be established throughout Egypt. BEIB has assisted the Ministry of Health in supplying the center with the necessary equipment and spare parts, and has to date trained two Ministry of Health personnel in the repair and maintenance of scientific and hospital equipment. The center, to be located in the governorate of Giza, is scheduled to open January 1, 1982.

Japan

As a result of a proposal by the U.S.-Japan Counterpart Working Group, which met as part of the U.S.-Japan Meeting on Research Cooperation in Science and Technology in February 1980, an international agreement between the two Governments was finalized which included a collaborative project in laboratory animal science. The agreement is entitled Agreement Between the Government of Japan and the Government of the United States of America on Cooperation in Research and Development in Science and Technology, April 14, 1980 (U.S.-Japan Non-Energy Cooperative). The purpose of the project is to promote the exchange of information on laboratory animal models, the development and use of uniform international standards for research animals, and the exchange of information on other aspects of laboratory animal science. The Division of Research Services was given responsibility for U.S. involvement in this project.

In May 1980, a joint meeting was held in the U.S. to plan for cooperation and future development of activities in the laboratory animal science project. It was decided that the initial thrust should be toward information on quality control of laboratory animals. The group agreed to encourage a series of workshops to pursue these topics with an ultimate goal of preparing a series of U.S./Japan Laboratory Animal Quality Control manuals. The first workshop was conducted on genetic monitoring and was held in Tokyo in July 1980, with active participation by representatives from both coun-

tries. A manual on genetic monitoring is nearing completion. In December 1980, the Japanese hosted the first meeting on microbiologic monitoring of laboratory animals. The United States will host a second meeting in San Francisco, December 14-16, 1981, to begin drafting a manual on monitoring of selected microbial agents that interfere with the use of laboratory rodents in biomedical research.

Activities with International Agencies

World Health Organization

The NIH genetic resource of laboratory rodents and rabbits has been designated as a WHO Collaborating Center for Defined Laboratory Animals, and as an international nude mouse reference center by the International Council on Laboratory Animal Science (ICLAS). The resource maintains over 200 stocks and strains of genetically and microbiologically defined rodents and rabbits and serves as a source of breeding nuclei of animals used by NIH research investigators as well as the international biomedical research community. Over 5,000 animals were supplied to domestic and foreign research institutions in FY 1981.

In late FY 1980, a contract was awarded to the World Health Organization (WHO) to develop an international primate supply program. WHO is to provide expert consultation and advisory assistance to the governments of interested countries in planning and implementing conservation measures, and ensuring the continuing availability of nonhuman primate species necessary for biomedical research. This contract is intended to implement recommendations made by the Interagency Primate Steering Committee as outlined in the *National Primate Plan*.

The National Institutes of Health (NIH) has a critical interest in the continuing supply of nonhuman primates. NIH intramural programs (including the Bureau of Biologics, FDA, needs of which are supplied through NIH) utilize more nonhuman primates than any other government organization. In addition, NIH extramurally supported research requires one-third of the total animals used for health-related programs. Another major user group is the pharmaceutical/biological industry, where nonhuman primates are required for the production and testing of drugs and biologic products that are licensed and controlled by the Food and Drug Administration. Because of the rapid decline of primate populations, and because of the importance of these animals to human, health-related needs, the objectives served by the WHO contract are of the utmost importance. It is hoped, through conservation management programs and the breeding of nonhuman primates under seminatural conditions in countries where they are indigenous, that surplus animals will be available for biomedical investigation without endangering native populations of animals.

Pan American Health Organization

The Interagency Primate Steering Committee, through a contract with the Pan American Health Organization (PAHO), has developed projects to establish New World primate breeding centers and conservation programs in Latin American countries. The majority of these countries imposed restrictions on the commercial export of nonhuman primates in 1973, and several have been interested in providing those species required for biomedical research through captive breeding and controlled wildlife management programs.

Specific objectives of the contract are:

- To provide expert consultants and advice to Latin American Governments interested in developing national primate programs as recommended by the World Health Organization;
- To assist in developing programs of wild primate conservation and management;
- To ensure the perpetuation of natural nonhuman primate resources; and
- To support development of primate breeding stations to produce species important to biomedical research under captive or semicaptive conditions.

The fully established Peruvian National Primate Project includes a breeding station in Iquitos, as well as field management activities. Tamarins and squirrel monkeys have been provided for use in U.S. biomedical activities since 1976. As a result of an agreement between PAHO and the Government of Colombia, a captive owl monkey breeding station was established at Armero, and an ongoing conservation program is being developed. It is anticipated that an agreement will also be undertaken to assist in coordinating primate breeding and conservation programs in Brazil. These programs will eventually become self-supporting through funds received for primates that are made available for scientific use.

Scientific Attache and International Health Representative to India

In January 1980, a senior staff member was detailed to the Department of State and has been assigned to the U.S. Embassy in New Delhi, India, as the U.S. Scientific Attache and International Health Representative. In this assignment, he assists the Scientific Counselor in all matters relating to U.S. scientific affairs in India, with specific responsibility for representing, monitoring, and coordinating the program interests of the U.S. Department of Health and Human Services and other U.S. agencies engaged in health and health-related activities. The appointment is important to the Department because of the interest in continuing collaborative health activities with India, particularly in view of the Department's policy to focus even greater attention and resources on health problems of the developing world.

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